Paid Circulation, 26,128

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 249 JULY 9, 1953 NUMBER 2

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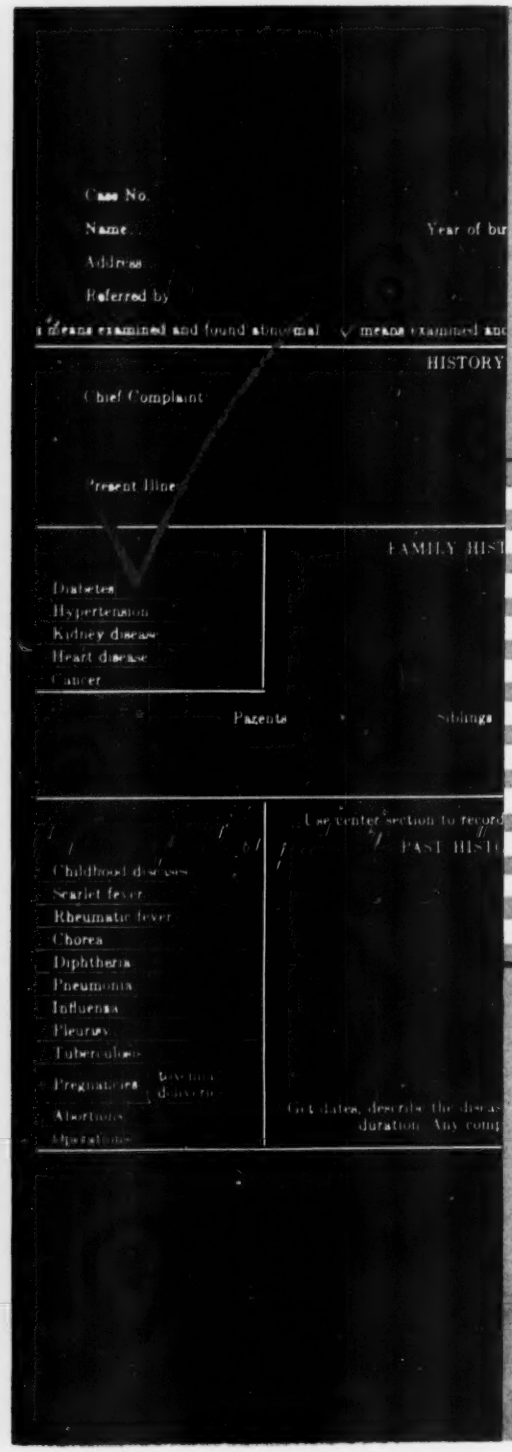

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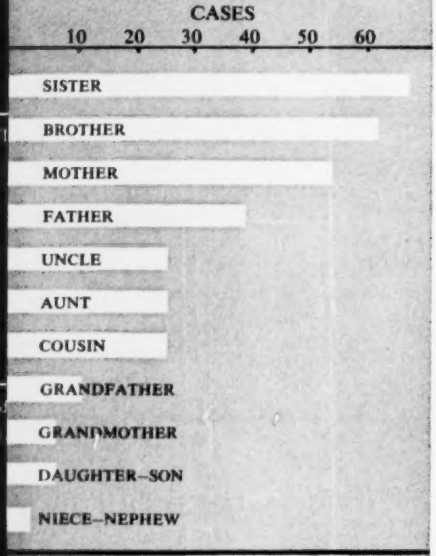

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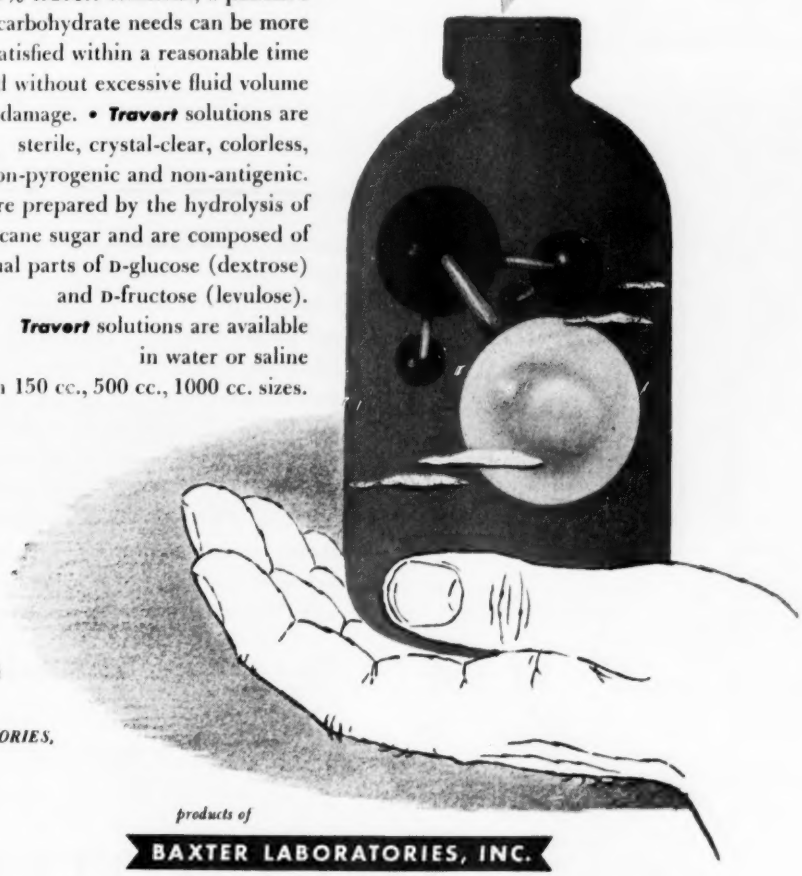

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2. *Wright, C. S. et al.: A. M. A. Arch. Dermat. & Syph. 67:125 (Feb.) 1953.*
3. *Robinson, H. M. et al.: South. M. J. (in press).*
4. *Andrews, G. C. et al.: J. A. M. A. 146:1107 (July 21) 1951.*

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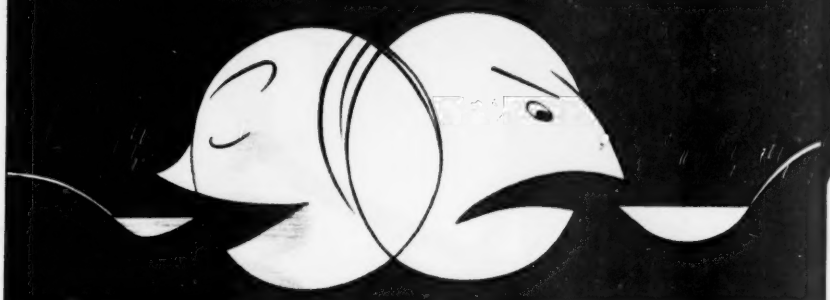

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Volume 249 JULY 9, 1953 Number 2

PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA)*

PAUL M. BEIGELMAN, M.D.,† FRED GOLDNER, JR., M.D.,‡ AND THEODORE B. BAYLES, M.D.§

BOSTON

THE skin manifestations of scleroderma have long been recognized and adequately described. These features are usually identified readily, particularly in the later phases of the disease when the spectacular, hardened, bound-down, wrinkleless appearance of the skin is so characteristic as to supply a descriptive name for the illness. This term refers to the most apparent manifestation of scleroderma and may, in part, explain the lack of emphasis on involvement of other body systems in the course of the disease.

As early as 1897, Hektoen[1] indicated that the disease was not limited to the skin. In a single case, he reported definite cardiac and endocrine lesions. More recently, series of cases have been reported establishing cardiovascular,[2, 3] gastrointestinal[4] and pulmonary[5, 6] involvement in scleroderma. Other protean manifestations of the disease, such as renal lesions,[7, 8] are now well documented. Hutcheson,[9] in 1951, reported cardiac, pulmonary or digestive gastrointestinal changes in 7 of 9 cases, with involvement of all three systems in 2 of these. The previous literature on scleroderma was thoroughly reviewed and interpreted by Beerman[10] in 1948.

Fifteen cases of scleroderma are described in this report. Five were studied post mortem, and their pathological and clinical findings correlated with those in other collagen diseases in an effort to elucidate certain factors pertaining to the pathogenesis of scleroderma.

TABLE 1. *Evaluation of Type, Age and Location of Onset in 15 Cases of Progressive Systemic Sclerosis (Scleroderma).*

CASE NO.	AGE AT ONSET	SEX	RACE	DURATION	EARLIEST SYMPTOMS	AREA OF SKIN FIRST INVOLVED
	yr.			yr.		
1*	52	F	W	11	Stiffness and swelling of joints of hands	Hands
2*	30	M	W	7	Joint swelling and pain	Fingers
3	47	F	W	4	Pain, swelling, stiffness of knee	Hand
4*	22	F	W	9	Joint pain and stiffness	Nose
5	37	F	W	3	Fever	Hands and forearms
6	46	F	C	10	Swelling, pain, tenseness and shininess of skin of fingers	Fingers
7	45	F	W	1	Joint swelling and pain	Fingers
8*	33	F	C	4	Felons of digits	Fingers
9*	41	F	W	4	Swelling of left side of face; headaches; vertigo, paresthesias of wrists.	Forearms and lower legs
10	42	M	W	3	Joint pains	Hands and feet
11	40	F	W	3	Redness and itching of neck	Neck
12	19	F	W	16	Change of color of hands (in cold)	Hands
13	34	F	C	3½	Pain, stiffness of joints of fingers	Fingers
14	33	F	W	3½	Vitiligo of cheeks, fingertips, upper chest and shoulders	Fingers
15*	39	M	W	6	Numbness of hands	Hands

*Patient deceased.

SYMPTOMS

All but 3 of the 15 patients in this series were women (3 were Negresses). The average age at onset was about forty, but this varied greatly. In 1 patient the first symptoms developed at the age of nineteen, whereas the illness of the oldest started at fifty-two. There was no relation between the age at onset and prognosis (Table 1). One patient was still living sixteen years after the first appearance of scleroderma, whereas others died in about four years.

The multiplicity of symptoms that were usually associated with organic disease was striking. All 15 patients had experienced some cutaneous alterations, and the change common to all was thickening of the skin. Six patients had noted vitiligo, and 6

*From the medical services of the Peter Bent Brigham and Robert Breck Brigham hospitals, and the Department of Medicine, Harvard Medical School.

†Senior assistant surgeon, Laboratory of Infectious Diseases, National Institutes of Health, Bethesda, Maryland; formerly, junior assistant resident in medicine, Peter Bent Brigham Hospital.

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12	19	F	W	16	Change of color of hands (in cold)	Hands
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§Clinical associate in medicine, Harvard Medical School; director of research and visiting physician, Robert Breck Brigham Hospital; associate in medicine, Peter Bent Brigham Hospital.

had observed hyperpigmentation. Two of those with vitiligo also had hyperpigmentation. Two patients had pruritus early in the disease, and alopecia developed in 2 female patients.

Constitutional symptoms, although variable in time of onset, were present in all patients. Twelve had lost weight, but this loss bore no direct relation to either dysphagia or anorexia. The rapidity of weight loss was quite variable and some patients actually gained weight during remissions. Nearly half the patients had noticed weakness or increased fatigability, and 6 were febrile.

Twelve patients had typical Raynaud's syndrome. It is of interest that 2 of the 3 men had classic Raynaud's symptoms. Twelve patients complained of joint pains or swelling or stiffness, or all three, at some time during the course of their illness. The joint changes clinically were usually different from those in uncomplicated rheumatoid arthritis, and the pathological findings were quite different.

During the course of the illness, 14 patients displayed some degree of cardiorespiratory embarrassment. It was often difficult to differentiate involvement of the two systems on the basis of symptoms. Nine complained of dyspnea, and 7 had ankle edema. Six patients had palpitations. Three were hoarse, without relation to any acute laryngeal infection.

Eleven had complaints referable to the gastrointestinal system. Eight noted dysphagia. None had urinary symptoms.

Although the course was often unpredictable and prognosis was difficult to estimate, it seemed apparent that multiple lesions of various body systems would eventually develop in all patients. The earliest symptom in 7 cases was referable to the joints rather than the skin. Seven other patients had skin manifestations as the initial evidence of the disease: some noted thickening of the skin first, whereas others had pruritus, erythema, vitiligo and, in 1 case, felons. Twelve patients had the earliest skin manifestations on their fingers or hands.

TABLE 2. *Roentgenologic Findings in 9 Cases of Progressive Systemic Sclerosis (Scleroderma).*

Case No.	Patient	Lungs	Heart	Esophagus	Bowel	Soft Tissues	Bones	Joints
1	A. Z.	Blunting of angles; pleural thickening; increased linear density at bases.	Triangular configuration	Dilated upper third	Deformed duodenal cap; atonic descending colon.	Calcification (fingers, wrists and feet)	Erosion of terminal phalanges	Flexion deformity of fingers
2	F. R.	Infarction pneumonitis	Normal	Narrowing, with proximal dilatation	Duodenal deformity; hyperactivity; segmentation; dilatation and ulceration of colon.	Calcific deposits	Normal	Normal
3	A. G.	Normal	Normal	Normal	Normal	Swelling at middle phalanges	Early demineralization of short middle phalanx of little fingers	Normal
4	R. S.	Normal	Normal	—	—	Atrophy of fingertips	Demineralization (hands); narrowing of ulna.	Dislocation; subluxation (hands).
8	J. W.	Fibrotic streaks at bases; fluid at bases.	Combined valvular disease and enlarged left atrium and pulmonic artery; heart enlarged.	Dilatation and diverticulum in 1946; none in 1948.	Agranular, dilated colon	Smooth	Partial loss of terminal phalanges; atrophy of disuse.	Filiform swelling of proximal interphalangeal joint.
9	T. K.	Basal streaking and nodularity	Triangular configuration; heart enlarged.	Atony	Atony; poor emptying.	Smooth	Decalcification	Flexion deformity
10	L. C.	Basal atelectasis; generalized nodularity and fibrosis, worse at bases.	Prominence of left ventricle, suggesting disease of aortic valve; later, cardiac enlargement.	Dilated, smooth constriction just above diaphragm	Normal	Smooth	Slight demineralization on slight rounding of tuft of right index finger	Flexion deformity
14	M. F.	Definite basal infiltration	Combined valvular disease; heart enlarged; configuration abnormal.	Atonic	Diverticulum of colon	Smooth; calcification.	Demineralization; terminal tuft changes.	Arthritic joint destruction; deformity of interphalangeal joints.
15	G. F.	Diffuse, coarse mottling in bases	Enlargement	Normal		Spindle-shaped periarticular swelling; calcium deposit in thumbs.	Decalcification	Narrowing of interphalangeal joints

Physical Signs

The findings on physical examination also represented manifestations of a diffuse pathologic process involving multiple systems, and these, for the most part, closely paralleled the subjective complaints. Physical examination revealed cutaneous changes

in all 15 patients. All had skin thickening, 10 showed hyperpigmentation, and 6 had vitiligo. Twelve demonstrated marked limitation of joint motion.

Eleven patients had systolic cardiac murmurs, and physical examination revealed cardiomegaly in 6. Gallop rhythm, pulsus alternans, pericardial friction rub and multiple arrhythmias were also noted. Abnormal pulmonary physical findings were present in 9 cases, the most common being rales, but dullness to percussion and abnormal breath sounds also occurred. There was 1 case of pleural friction rub.

Laboratory Findings

The laboratory findings were of relatively little importance in the diagnosis of diffuse scleroderma.

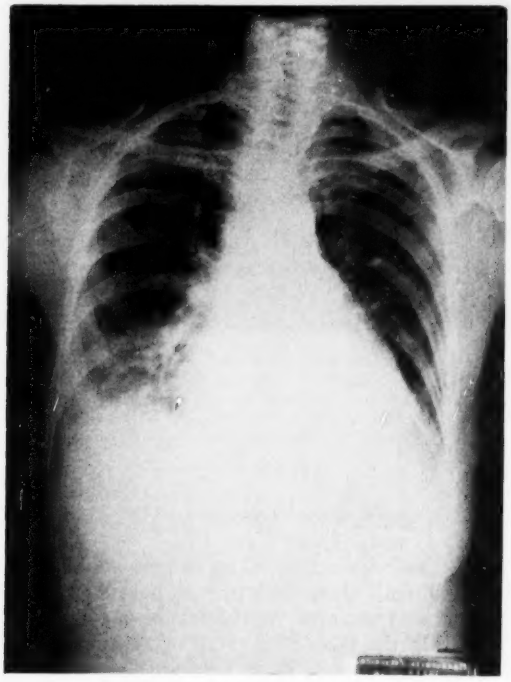

Figure 1. *Roentgenogram in Case 14, Taken in October, 1950, Showing Cardiac Enlargement, with the Configuration of Combined Valvular Disease, and Definite Infiltration of the Right Base.*

Eight of the patients demonstrated an anemia at some time during the course of the disease. Of these, 3 had a hematocrit above 37 per cent.

An elevated erythrocyte sedimentation rate was a common finding in scleroderma, occurring in 11 cases. The white blood cells were normal. As noted above, these patients were free of urinary signs and symptoms, despite proteinuria, usually mild, in 8 cases.

Five of 11 patients with albumin-globulin determinations showed hyperglobulinemia and reversal of ratio. The speed with which this reversal occurred appears to have had little prognostic value. Only 1 of 8 subjects with serum calcium determinations had a value below normal.

Low vital capacity in scleroderma could not be attributed solely to pulmonary fibrosis since many patients had pulmonary edema. In addition, involvement of the thoracic muscles, the diaphragm

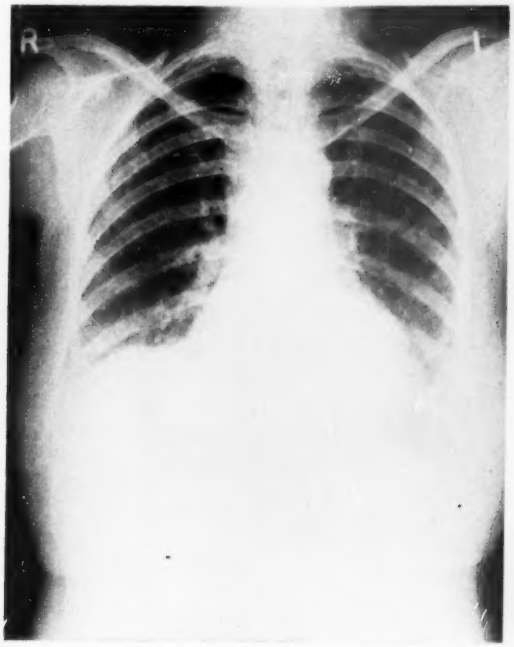

Figure 2. *Roentgenogram in Case 9, Taken in September, 1946, Showing Enlargement of the Heart to the Right and Left, with a Triangular Configuration and Nodular Streaking Infiltration at Both Lung Bases.*

or the skin of the chest might well account for a diminution in vital capacity.

Roentgenologic Findings*

Thorough radiologic studies were performed in 9 cases, multiple system involvement being visible in 8 (Table 2). Five patients displayed lesions of the heart, lungs, gastrointestinal tract, joints or bones and soft tissues. Seven revealed definite pulmonary abnormalities, chiefly nodular, and linear streaking at the bases. Cardiac changes were visible in 6 cases. The configuration appeared to be combined valvular disease, which was observed in 2 cases (Fig. 1), and a somewhat unusual triangular cardiac silhouette, which was present in 2 others (Fig. 2). Esophageal lesions, ranging from con-

*Milton Elkin, M.D., of the Department of Radiology, Peter Bent Brigham Hospital, reviewed the roentgenograms.

striction to atony or dilatation, were noted in 6 cases (Fig. 3).

Bony changes were evident in 8 cases, demineralization occurring in 7, and terminal-tuft changes in 3. Erosion of the fingertips was present in 2 cases. Flexion deformity, similar to that observed in rheumatoid arthritis, was also evident, typical changes occurring in 2 cases (Fig. 4).

FIGURE 3. *Roentgenogram in Case 12, Taken in February, 1950, Showing the Esophagus to Be Dilated and Smooth, with a Constriction Just above the Diaphragm.*

There was typical smoothing of the skin folds in many cases. Calcification of the soft tissues was evident in 4.

ELECTROCARDIOGRAPHIC STUDIES*

Fourteen patients in the series had electrocardiographic studies, some with multiple tracings at frequent intervals. No characteristic or definitive changes particularly diagnostic of scleroderma were noted. Most of the findings were nonspecific, including T-wave inversion, prolongation of the QT interval, low electromotive force and various arrhythmias. Although the electrocardiogram in scleroderma may be normal, it more commonly exhibits changes in the T wave, usually flattening or inversion or QT-interval prolongation, or cardiac arrhythmias, principally premature beats.

Absence or diminution of R-wave amplitude in the precordial leads usually suggests myocardial infarction. In the absence of RS-T-segment deviation or of T-wave inversion, it may denote old healed myocardial infarction. It is the absence of healthy myocardium and its ability to respond to the activating impulse that accounts for this electric phenomenon. Although this is usually the sequence of myocardial infarction from either coronary-artery disease or deficient coronary-artery perfusion, it can result from other conditions, including amyloidosis,[11] certain types of constrictive pericarditis[12] or, as in Cases 1, 9 and 15, scleroderma (Fig. 5 and 6). Advanced sclerodermatous myocardial changes were demonstrated in 2 of these cases at autopsy (Cases 9 and 15).

FIGURE 4. *Film of the Hands in Case 1, Showing Marked Flexion Deformity of the Fingers, Calcifications in the Soft Tissue (Particularly in the Ulnar Portion of the Left Wrist and the Terminal Portion of the Right Thumb), Erosion of the Terminal Phalanges, Bony Demineralization and Marked Soft-Tissue Atrophy.*

Three patients exhibited no electrocardiographic abnormalities. One, with initial normal tracings later showed changes in the ST segment and T waves. On the basis of a small or absent R wave in Leads V_1 through V_4 in 2 cases, the possibility arose that there was a displacement of the transitional zone to the left, and cor pulmonale was suggested. One of these cases (Case 9) exhibited myocardial and pulmonary changes at autopsy.

Four patients demonstrating electrocardiographic abnormalities were receiving adrenocorticotrophic hormone (ACTH) or cortisone concurrently. In 2 of these cases (1 and 15), the progression and regression of certain arrhythmias seemed to parallel the institution and discontinuance of hormone therapy.

In 5 of the 6 fatal cases (Cases 1, 2, 4, 9 and 15) the electrocardiogram exhibited profound changes, simulating myocardial infarction in 3. Such find-

*We are indebted to Harold D. Levine, M.D., of the Department of Medicine, Peter Bent Brigham Hospital, for Figures 5 and 6, and for his collaboration in preparing the text of this section.

ings are obviously associated with severe cardiac disease as an expression of generalized progressive visceral scleroderma.

Pathology

At autopsy all 5 fatal cases exhibited typical sclerodermatous skin changes. Three of the 5 patients were cachectic at time of necropsy. The microscopical changes in the systemic lesions were usually much more striking than the gross findings (Table 3).

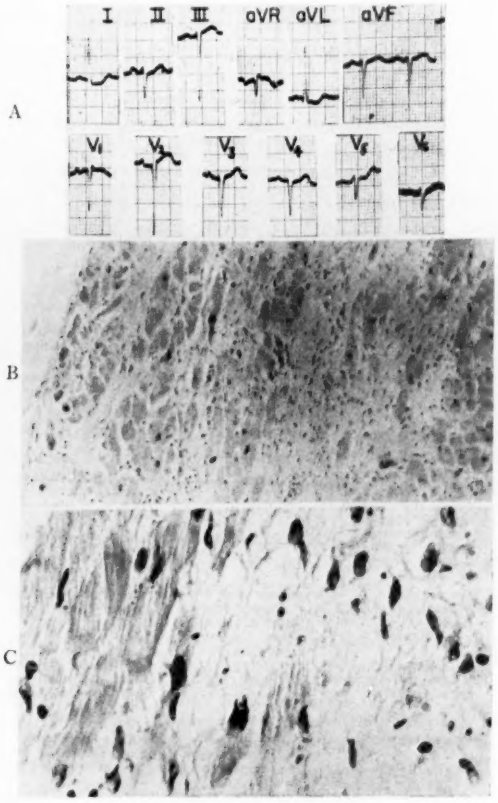

Figure 5. *Electrocardiographic Pattern and Histologic Appearance of the Heart in Case 9.*

A = electrocardiograms, showing diminutive R waves in the precordial leads compatible with old anteroseptal infarction. B = low-power photomicrograph (approximately X60) of subendocardial part of interventricular septum, showing fibrous-tissue encroachment on the myocardium. C = high-power detail of the same specimen (approximately X200). Note the stifling of myocardial fibers by fibrous connective tissue. Similar areas were scattered through the free walls of the ventricles, some subendocardially, some subepicardially and some midway in the thickness of the ventricular walls. (Myocardial scarring of this type has a similar electric effect to that after myocardial infarction from coronary-artery disease.)

There was microscopical myocardial fibrosis in all 5 cases (Fig. 5), pleural and pericardial thickening in 4, and endocardial or valvular fibrosis in 4. Three patients showed fibrosis of both the pulmonary parenchyma and of some portion of the gastrointestinal tract (Cases 8, 9 and 15). An additional patient (Case 4) had pulmonary fibrosis, and another (Case 2) gastrointestinal fibrosis. Three cases revealed esophageal fibrosis. The fibrotic lung lesions in 3 cases were nonspecific, but unique cystic changes (Fig. 7) were evident in the fourth (Case 15).

Definite renal and hepatic fibrosis occurred in Cases 2 and 9. Vascular changes were ubiquitous in multiple organ systems in all cases. The pathological pattern emerging was mainly that of intimal proliferation and of medial sclerosis. The most advanced changes were observed in Case 4, in which ACTH therapy was complicated by malignant hypertension, and in Case 15, with its neat correlation of parenchymal fibrotic and vascular lesions.

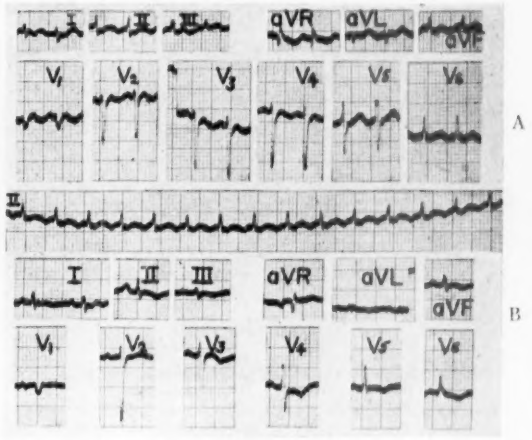

Figure 6. *Nonspecific Electrocardiographic Changes in the Heart in Scleroderma.*

A = initial tracings, showing auricular flutter with 2:1 response. B = tracings recorded on the following day, showing reversion to normal sinus rhythm and emergence of inverted T waves. This change is equivocal in significance, but it is compatible, among other possible causes, with myocardial ischemia, myocarditis and so forth.

Major gross findings included cardiac enlargement in 4 cases, joint changes in 2, excessive peritoneal fluid in 2 and pericardial effusion in 1. Emboli and infarcts to the pulmonary artery were observed in Case 2, and gross nodularity of the mitral and tricuspid valves in Case 8.

Therapy

The list of drugs employed, with consistently negative results, in the present series of cases includes metals (gold, arsenic, bismuth and iron), hormone preparations (thyroid, stilbestrol, relaxin,

testosterone and A.T. 10), vitamins (ascorbic acid, nicotinic acid and vitamin D), peripheral vasodilators (papaverine and Priscoline), penicillin, salicylates, neostigmine, Benadryl, para-aminobenzoic acid and ergostanyl acetate. Low-salt and high-protein diets were also ineffective. Similarly, spray radiation therapy and stellate-ganglion block were found to be of no value. Sympathectomy performed on 3 subjects gave relief, but only for four to six months.

ACTH and cortisone therapy was instituted in 9 cases. Duration of therapy and dosage were within the estimated effective nontoxic range. In 8 cases no more than mild, transient improvement could be attributed to these agents. Furthermore, severe hypertension and nephrosclerosis developed immediately after ACTH therapy in 1 patient (Case 4) who died from a cerebrovascular hemorrhage. Cardiac arrhythmias were aggravated by this form of treatment in 2 cases (Cases 1 and 15). One patient (Case 10) seems to have been benefited by maintenance therapy with cortisone over a thirty-month period.

Discussion

The wide variations in the symptomatology of scleroderma and its unpredictable course can be readily understood if one considers the basic pathologic process — a relentless and progressive involvement of most connective-tissue structures. Even ocular changes[13] and buccal lesions have been reported.[14, 15] In this series, as well as in most previous reports, the initial changes appeared invariably in the skin. Cases in which dysphagia and cardiac embarrassment were the first indications of the disease[2] must be considered as exceptional ones. In the early phases of scleroderma cutaneous alterations dominate the clinical picture. They remain conspicuous throughout the course of the disease, but are later overshadowed by much more serious lesions in the cardiovascular, respiratory, digestive and other systems. Table 3, correlating clinical data in 5 autopsied cases with post-mortem findings, illustrates this point. It indicates that widespread and advanced changes in the connective tissue correspond to clinical observations, including

Table 3. *Correlation of Clinical, Electrocardiographic, Radiologic and Pathological Findings in 5 Autopsied Cases of Progressive Systemic Sclerosis (Scleroderma).*

Case No.	Pathological Findings		Systemic Involvement	X-Ray Findings	Electrocardiographic Findings	Related Clinical Findings
	gross	microscopical				
2	Enlarged heart	Pericarditis, myocardial fibrosis	Cardiac	Negative	Nonspecific T-wave change	Dyspnea and ankle edema; palpitation.
	Pulmonary infarction	No pulmonary fibrosis	Pulmonary	Possible infarction	—	Chest pain
	Dilatation of esophagus	Esophageal fibrosis; intestinal fibrosis.	Gastrointestinal	Esophageal narrowing, with proximal dilatation and segmentation; hypomotility; ulceration of colon.	—	Nausea and vomiting; dysphagia; constipation.
4	Myocardial fibrosis	Myocardial fibrosis	Cardiac	Negative	RVH, nonspecific	Dyspnea
	—	Pulmonary fibrosis	Pulmonary	Negative	T-wave changes	—
	—	—	Gastrointestinal	Negative	Q wave prolonged in Lead V_4	Nausea and vomiting
8	Enlarged heart; inflammation of mitral and tricuspid valves.	Myocardial fibrosis; valvulitis.	Cardiac	Combined valvular disease (triangular configuration)	Low or inverted T waves; ST-segment depression.	Ankle edema; dyspnea; chest pain; palpitation.
	Pleuropericardial adhesions; pleural thickening.	Pulmonary fibrosis	Pulmonary	Infiltration at lung bases	—	—
	—	Esophageal and intestinal fibrosis	Gastrointestinal	Diverticulum and dilatation of esophagus in 1945; normal in 1948; 1946 — abnormal segmentation, dilated colon, duodenal diverticulum.	—	Nausea and vomiting; dysphagia; anorexia.
9	Enlarged heart; pleuropericardial thickening.	Fibrosis; pleuropericardial thickening.	Cardiac	Triangular configuration; enlarged heart.	Premature ventricular beats; hypertrophy of left ventricle; acute cor pulmonale.	Ankle edema; palpitation; dyspnea.
	Atelectasis, adhesions	Pulmonary fibrosis	Pulmonary	Fibrotic streaking	—	—
	Areas of dilatation; plaques in wall of gastrointestinal tract.	Esophageal and intestinal fibrosis	Gastrointestinal	Intestinal and esophageal atony	—	Nausea and vomiting; dysphagia; constipation.
15	Enlarged heart; pericardial effusion.	Myocardial fibrosis	Cardiac	Enlarged heart	Auricular flutter. Multifocal repetitive premature beats.	Dyspnea; cough; ankle edema.
	—	—	—	—	Posterior myocardial infarct; old changes.	—
	Fibrosis	Fibrosis; cysts.	Pulmonary	Fibrotic mottling	—	Dyspnea; cough.

electrocardiographic and roentgenologic findings. All 5 patients were dyspneic, and 3 had palpitations. Myocardial fibrosis was noted in all at autopsy. Three patients with dysphagia had similar changes in the esophageal connective tissue. In 2 of the 3 patients with persistent constipation, intestinal fibrosis was revealed at autopsy.

The term scleroderma may be considered a misnomer and has been, in part, responsible for the excessive emphasis placed on the cutaneous lesions. Progressive systemic sclerosis, proposed by Goetz,[3, 16] would be more suitable.

The attempt to establish a presumably milder form of the disease, a localized scleroderma accompanied by symptoms of Raynaud's disease (acrosclerosis of O'Leary[17, 18]), found no support in this study. The presence or absence of these peripheral vascular changes proved to be of little prognostic value in the present series of cases.

It is a matter of common knowledge that in the course of scleroderma marked exacerbations and remissions are frequently observed. In the past, these fluctuations, at times associated with menstruation or pregnancy, have led many investigators to invoke an endocrine dysfunction as the prime etiologic factor in scleroderma. Some authors have described microscopic lesions in the pituitary or thyroid gland.[1] Others have noted an altered calcium balance[19]; some have reported in the female patients evidences of ovarian hypofunction,[20] and, more recently, hypoadrenalism, as indicated by low 17-ketosteroid excretion or a positive Kepler–Power water test, has been implicated.[21] Certainly, these observations are neither frequent nor consistent enough to permit any etiologic considerations.

On the other hand, one may be justified in postulating certain mechanisms possibly involved in the pathogenesis of progressive systemic sclerosis, particularly when this entity is considered in its relation to the entire family of collagen diseases.

The hypothesis has been presented in a recent study of platelet thrombosis[22] that the site of an antigen-antibody allergic type of reaction may be decisive in determining its clinical and pathological manifestations. On the basis of this report, of earlier work by Pagel[23] and of unpublished studies by Friedman,[24] it was proposed that a subintimal location of the reaction resulted in platelet thrombosis, that primary medial involvement occurred in periarteritis nodosa, and that acute disseminated lupus erythematosus was an expression of mesenchymal reaction and damage.

The histologic findings in the present series, which confirm primary and basic involvement of connective tissue, place this disease, pathogenetically, in the same group with disseminated lupus erythematosus. The major difference in the clinical picture and course of the two diseases can be perhaps explained through the influence of factors other than the site of reaction — namely, differences in the intensity and diffuseness of the reaction. Just as platelet thrombosis indicates a generalized fulminant, subintimal reaction, contrasted to the localized necrotic lesions described by Pagel and deriving from a low-grade smouldering process, so acute disseminated lupus suggests a comparatively severe, rapid connective-tissue reaction, with edema and necrosis predominating, and progressive systemic sclerosis (scleroderma) represents a slow, torpid, generalized mesenchymal response, with fibrosis and sclerosis predominating. The ubiquitous proliferative hyaline vascular lesions

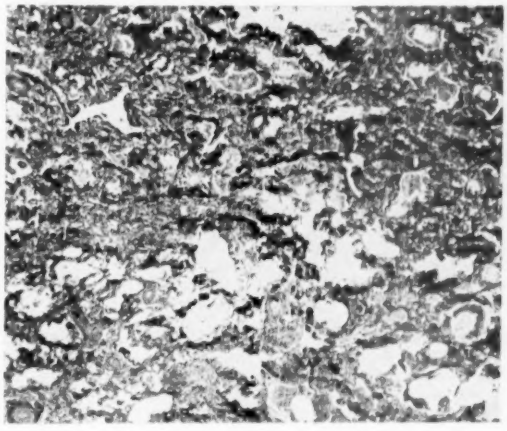

FIGURE 7. *Section of the Lung in Case 15, Showing Severe Fibrosis, Bullous Cavitation and Marked Arterial Intimal Hyperplasia (X15).*

observed in this series were probably sequelae of early, mild vessel-wall reaction preceding mesenchymal involvement. The presence of striking sclerodermatous vascular lesions has been emphasized by others.[25] Kampmeier[26] has already suggested that the intensity and location of collagen-disease reaction, presumably allergic, determines the particular expression of illness, periarteritis nodosa representing one extreme and scleroderma the other.

Case 14 presents an interesting clinical expression of a possible intermediate grade of reaction. The fever, marked anemia and miliary telangiectatic skin eruption suggest an acute disseminated lupus erythematosus type of syndrome, whereas the skin and esophageal lesions and the long duration of the illness are characteristic of progressive systemic sclerosis.

Moreover, combinations or overlapping of entities has been observed on occasion among the collagen diseases. The overt features of intimal involvement (platelet thrombosis) and mesenchymal reaction (acute disseminated lupus erythematosus) may coexist.[22] Periarteritis nodosa, principally a vascular

medial lesion, and platelet thrombosis may occur simultaneously.[27] A single case presented the pathological stigmas of Libman–Sacks disease, periarteritis nodosa, scleroderma, dermatomyositis, lupus erythematosus, rheumatic infection and rheumatoid arthritis.[26] Another case[28] presented, simultaneously, stigmas of polyarteritis nodosa, disseminated platelet thrombosis and disseminated lupus erythematosus; lesions of malignant hypertension, pulmonary silicotuberculosis and sarcoidosis-like lymphadenopathy were also reported.

In a case of scleroderma Pagel[25] found histologic changes "indistinguishable" from those of disseminated lupus erythematosus and polyarteritis nodosa. He presented other histologic evidence of the essential unity of these diseases, which he designated as the rheumatic and para-rheumatic group.[29] On the basis of these and additional observations, Pagel[30] has stated agreement with the hypothesis outlined in this discussion.

Fifteen cases of scleroderma are described below. Five were studied at autopsy, and correlation of their pathologic and clinical findings with those noted in other collagen diseases may help to elucidate certain factors pertaining to the pathogenesis of scleroderma.

Case Reports

Case 1. In 1941, A. Z. (R.B.B.H. 3518), a 52-year-old woman, had an illness characterized by stiffness, pain, swelling and tenderness of the joints, elevated sedimentation rate, and rapid loss of 25 pounds in weight that was diagnosed as rheumatoid arthritis in another hospital. A subtotal thyroidectomy for nontoxic goiter had recently been performed. Chronic vomiting of unknown cause had been present for 20 years. There was a precordial systolic murmur, loudest at the apex. Roentgenograms revealed a few punched-out areas in the articulating bones of the hands and wrists. Stiff, cold, blue phalanges and forearms were suggestive of scleroderma.

During the following 3 years, a harsh productive cough persisting for several weeks, a weight loss of 63 pounds in 1 year, slight edema, some dyspnea, hyporexia and typical Raynaud's symptoms developed. By 1944, shiny, tight, hard, varnish-like skin diagnostic of scleroderma was noted over the face and extremities, and there was definite clubbing of the terminal phalanges (Fig. 4). Mild congestive heart failure was treated successfully.

Weight loss continued, and epigastric pain began in September, 1945. Radiologic studies disclosed a widened esophagus, a large stomach, with retention, and a probable active gastric ulcer.

Steady deterioration continued, and by March, 1946, additional complaints included orthopnea, bone pain, frontal headache and dysphagia. By this time, the fixed, tight skin was brownish, the mouth could not be opened widely, cardiomegaly was present, there was lower-lobe pulmonary fibrosis, and no peripheral pulses were palpable. Roentgenograms revealed esophageal changes consistent with scleroderma. Electrocardiograms showed premature ventricular beats, low voltage, and QRS-segment and T-wave changes. A skin biopsy demonstrated pathological changes consistent with scleroderma.

The patient became extremely emaciated and tachypneic in September, 1948, and for the first time there were atrophic ulcers over the knuckles and toes, and the atrophic terminal portions of the cold fingers were in fixed flexion. Liver extract, nicotinic acid and Fowler's solution by mouth were ineffective.

The slow, inexorable, downhill course continued during the succeeding 2½ years. Localized constricting chest pain and diarrhea began early in 1950. Courses of cortisone and ACTH in October, 1949, the occasion of her first entry to the Robert Breck Brigham Hospital,[31] and again in September and October, 1950, brought only partial, temporary relief. Serious cardiac arrhythmias occurred in October, but these subsided with cessation of cortisone therapy and institution of quinidine. The patient was not under medical observation during the last few months of her life. She died in March or April, 1951. There is no record of the terminal episode.

This case was of at least ten years' duration, far-advanced lesions and serious debility being evident for approximately seven years.

Case 2.* F. R. (R.B.B.H. 3512), a 37-year-old truck driver, entered the hospital in September, 1949, with intermittent joint swelling and pain of the extremities, which had begun 2 months after his induction into the Army in 1942. Shortly afterward, he noted gradual thickening of the skin over the fingers, with limitation of finger motion and numbness, blueness and coldness of the knees on exposure. In 1943 intermittent epigastric pain, relieved by food or alkali, began. Dysphagia, esophageal stricture, diagnosed radiologically, and weight loss (totaling 40 pounds by 1949) also appeared at this time.

Between January and June, 1949, the patient had headache, blurred vision and a mild transient hemiparesis. Findings at another hospital included a blood pressure of 189/110, Grade 3 hypertensive retinopathy with papilledema, a Grade 1 apical systolic precordial murmur, epigastric tenderness and hard, nonmobile skin over the fingers, with limitation in motion of the terminal phalangeal joints.

Examination of the blood revealed a hemoglobin of 9.4 gm. per 100 cc. and a nonprotein nitrogen of 52 mg. per 100 cc.; the stools were guaiac positive. The 2-hour phenolsulfonephthalein excretion was 38 per cent. An electrocardiogram indicated hypertrophy of the left ventricle. Roentgenograms showed stasis, marked atony and dilatation of the stomach and intestines in addition to the esophageal abnormalities previously observed.

Shortly after admission marked temporary relief was obtained, and further improvement followed a 3-week course of ACTH.[31] However, the patient died on December 27 at another hospital. Severe pulmonary edema and fever were the dominant features of the terminal episode.

At autopsy, gross examination demonstrated 550 cc. of fluid in the right pleural sac. Pleural and pericardial adhesions were evident. The left upper pulmonary lobe contained several fresh, wedge-shaped, subpleural infarcts, and there were numerous reddish-gray emboli. The heart was moderately hypertrophied, weighing 560 gm., and contained a firmly adherent, grayish-red thrombus in the right atrium. The spleen, which weighed 275 gm., had many gray-yellow, capsular, fibrinous adhesions. The esophagus was markedly dilated, with a thin wall containing many shallow erosions in its lower third, and was contracted 3 cm. proximal to the cardioesophageal junction. The right kidney, weighing 180 gm., and the left, weighing 80 gm., exhibited red and yellow cortical streaking.

Microscopical examination showed the pulmonary blood vessels to be engorged. Pink precipitate was present in many alveoli. Considerable neutrophilic infiltration was noted in one lung section, adjacent regions exhibiting hemorrhage and necrosis. Several medium-sized pulmonary arteries contained recanalized thrombi. The pleuras showed fibrous thickening.

The left ventricle and interventricular septum contained small patches of fibrosis. There was fibrous thickening of the small arteries and organizing, granular, hyaline thrombi in the small veins of the myocardium. A large thrombus was noted in the right auricular appendage. There was fibrous thickening of the visceral pericardium.

The spleen exhibited foci of fibrosis and large zones of necrosis packed with erythrocytes and fibrin, and there were several medium-sized venous thrombi. The central portions of the hepatic lobules were occupied by condensed stroma and hemosiderin-laden phagocytes. There was marked submucosal fibrosis and variable atrophy, fibrosis and degeneration of the smooth-muscle layers throughout the gastrointestinal tract. Fibrosis also involved the esophageal mucosa and the serosa of the colon. The small arteries and arterioles were thickened, particularly in the jejunum and colon.

Considerable fibrosis of the kidneys, bladder, perineural structures and perirenal fat was noted. There was atrophy of striated muscle. The dermis was markedly thickened by dense, acellular collagen, with atrophy of the epidermis and sweat glands, flatten-

*We wish to express our gratitude to Maurice B. Strauss, M.D., chief of medicine, for permission to publish clinical data from Cushing Veterans Administration Hospital, and to Robert Fienberg, M.D., chief of the Laboratory Service, for furnishing us a copy of the autopsy protocol.

ing of the rete pegs and fibrotic thickening of the arteries and arterioles. Fibrosis and atrophy of subcutaneous fat was evident.

The principal pathological diagnoses were diffuse scleroderma, failure of the left ventricle, pulmonary congestion and pulmonary infarction and emboli.

This patient had long-standing, diffuse, progressive scleroderma, confirmed by autopsy, but the severe hypertensive disease and pulmonary emboli were probably the immediate causes of death.

CASE 3. A. G. (R.B.B.H. 3254), a 51-year-old married seamstress, began to note fatigue and lassitude coincident with the gradual onset of joint swelling, pain and stiffness early in 1947. The hands were involved first, the knees and feet soon becoming affected. She was admitted to the hospital with a diagnosis of rheumatoid arthritis in October, 1947; scleroderma was recognized. She was unable to comb her hair or clench her fists; numbness and tingling of the extremities were present; there was brownish induration of the tight, waxy, nonelastic skin of the extremities, and slight cyanosis of the fingertips was observed. There was a Grade 1 apical systolic murmur and + pitting dependent edema. There was marked emotional instability. The only suggestive laboratory findings were an erythrocyte sedimentation rate of 0.45 mm. per minute and an albumin-globulin ratio of 3.3:3.0.

Subsequent therapy included gold, Fowler's solution, nicotinic acid, salicylates, Priscoline, vitamins and stilbestrol. There was moderate subjective and slight objective improvement during the next 2 years. A short course of ACTH in 1949 induced a temporary remission.[31] At that time the albumin-globulin ratio was 3.7:3.4, roentgenograms revealed mixed hypertrophic and rheumatoid arthritic changes of the hands and wrists, with the latter predominating, and skin biopsies showed pathological changes consistent with scleroderma. A spontaneous remission of pain occurred in the following year, and in the last 3 years the condition has not progressed.

CASE 4. R. S. (R.B.B.H. 2991), a 31-year-old divorced waitress, entered the hospital in October, 1945, with a 3-year history of joint pain and stiffness, beginning 2 weeks after severe laceration and apparent infection of a finger. Swelling of the fingers of both hands and dysphagia appeared soon afterward. The blood sedimentation rate had been 1.4 mm. per minute in 1943 at another hospital.

Physical examination showed tenseness and hardness of the skin over the phalanges, auricles and nose and subcutaneous calcinosis of the buttocks. There was also tenderness and ankylosis of all joints, the fingers and wrists being particularly affected.

Twelve pounds were lost between 1945 and 1949, when dyspnea and hyporexia began. In July, 1949, the joint pain became severe, and was unresponsive to aspirin or Demerol. The patient was markedly cachectic by October.

Therapy, including penicillin, sex hormones, extraction of teeth, papaverine and prostigmine, was ineffective. ACTH therapy in October, 1949, induced a temporary remission,[31] but hypertension (blood pressure of 175/95) supervened in January, 1950, accompanied by vertigo and blurring. A few days later, the patient suffered a cerebrovascular accident marked by nausea, vomiting, disorientation, elevated spinal-fluid pressure, Cheyne–Stokes respirations, left hemiplegia and microscopical hematuria and albuminuria. Her condition improved during the next 2 weeks, but she died 4 days after a second attack. The nonprotein nitrogen was 50.5 mg. per 100 cc., but other laboratory data, including an albumin-globulin ratio of 4.8:2.6, were normal. An electrocardiogram revealed left-axis deviation and, later, right-bundle-branch block.

At post-mortem examination the emaciated cadaver weighed only 85 pounds, with bronzed, tight, shiny skin and ankylosis and deformity of many joints. The heart, which weighed 360 gm., showed finely streaked white areas in the purplish-red myocardium. There was a 1-cm. dark-red area of hemorrhage in the left cerebral hemisphere.

Microscopical examination demonstrated myocardial and endocardial fibrosis, occasionally incorporating small groups of well preserved myocardial fibers. Moderate patchy subintimal aortic thickening by fibrous tissue and by small areas of amorphous eosinophilic material was noted. There was marked focal pleural, intra-alveolar and pulmonary perivascular fibrosis. Diffuse engorgement and, in 1 section, focal hemorrhage and necrosis, were evident in the lungs. There were moderate fibrous thickening and slight intimal proliferation of small pulmonary arteries.

Severe renal arterial and arteriolar intimal proliferation, with occasional disruption of the entire vessel wall, was evident. The afferent renal arteriolar walls exhibited swelling, eosinophilia and diminution of lumen size. There were submucosal hemorrhage, engorgement and fibrous thickening of the bladder. A 4-mm. area of localized hyperplasia, chiefly chromophobe cells, was present over the superior aspect of the anterior hypophysis. A large amount of fibrous tissue compressed the glandular elements of the breast. The knee-joint surfaces were focally interrupted by a small amount of irregular basophilic material, with thin, poorly staining, underlying cartilage, and interruption of the subchondral bone by fibrous tissue. The corium of the skin was composed almost entirely of dense collagen, with small fragments of elastic tissue, and the sudoriferous glands appeared to be compressed.

The principal pathological diagnoses were diffuse, generalized scleroderma, myocardial fibrosis, cerebrovascular hemorrhage and renal arteriosclerosis and necrosis.

This patient had severe, progressive, generalized scleroderma, with marked joint involvement. The immediate cause of death appears to have been a stroke secondary to hypertensive disease. This was probably a complication of ACTH therapy, and parallels the sequence of events and pathological findings in 2 other cases of scleroderma treated with ACTH.[32, 33]

CASE 5. M. H. (P.B.B.H. 10675), a 40-year-old married dress cutter, entered the hospital in July, 1943, with a 2-year history of cold sensitivity and cyanosis involving the fingertips and palms, increasing stiffness of the fingers, smooth, shiny, scaly, firmness of the skin over the dorsa of the hands and forearms, and slight increase in pigmentation. The last became quite marked in the following 6 months. Severe fatigue began 6 months later, but a hemoglobin of 40 per cent noted 3 months before admission supposedly responded to liver, iron and vitamin therapy.

Physical examination showed the skin to be darkly pigmented, chiefly over the arms, and demonstrated varying degrees of tenseness, induration and immobility, particularly over the shiny fingers and forearms. The skin over the fingertips and metacarpophalangeal joints was atrophic, red and smooth. Subcutaneous and interosseous atrophy involved the hands. There were Grade 1 apical systolic and Grade 2 basal systolic murmurs.

Laboratory and electrocardiographic studies were within normal limits aside from a sedimentation rate of 28 mm. per hour, a 17-ketosteroid level of 3.28 mg. per 24 hours and a vital capacity of 1700 cc. Roentgenograms revealed small fibrotic apical lesions consistent with old minimal pulmonary tuberculosis, atrophy of the bones of the hands and increased rigidity of the esophagus.

CASE 6. O.F.J. (P.B.B.H. 19253), a 56-year-old widowed Negress, was admitted to the hospital in November 1938, with a history of thyroidectomy in 1921, complicated by an episode of probable hypoparathyroidism. The family history included death of the subject's mother from "stricture of the throat," rheumatic fever in a daughter and exophthalmic goiter in a brother and both his daughters. In 1935, after great emotional distress over her mother's death, the patient began to have amenorrhea, palpitation, hot flashes, scattered increase in pigmentation, facial vitiligo, ankle pain and fatigue. Swelling, pain and numbness of the fingers, which later became tense and shiny, were also noted. After her husband's death, 2 years later, which also caused great emotional distress, exertional dyspnea and leg swelling began, and the patient was digitalized. About 1 year later, coldness of the extremities developed, and scleroderma was diagnosed. Within a few years, the fingers became fixed in partial flexion, and recurrent post-traumatic ulcers of the lateral malleoli developed; she lost 18 pounds in weight between 1943 and 1945. Constipation and dysphagia were additional complaints on readmission to the hospital in June, 1945.

Physical examination revealed an emaciated and tachypneic woman, with tight, mask-like facies, dry, hard, inelastic skin, scattered increased pigmentation, facial vitiligo, apical pulmonary

dullness, basal pulmonary rales, cardiomegaly, a pericardial friction rub, a questionable presystolic apical murmur and totally irregular cardiac rhythm. The scalp hair was dry and thinning, almost to baldness. The terminal phalanges were less than half the normal length, and the extremities and mandible showed marked loss of motion. Digitalis, Mercupurin and ammonium chloride were administered. The cardiac rhythm had reverted to normal. Thyroid, AT 10 and iron were additional medicaments.

At this time the urine gave a + to +++ test for protein, possibly because of transient cystitis. The sedimentation rate was 1.7 mm. per minute. White-cell counts varied from 12,000 to 22,000; the red-cell count was 3,980,000, with a hemoglobin of 9.9 gm. per 100 cc. and a hematocrit of 29 per cent. The albumin-globulin ratio was 3.3:4.8. Determinations of the basal metabolic rate were +14 and +12 per cent. Electrocardiograms revealed auricular fibrillation, premature ventricular beats and an abnormal ventricular complex. The last persisted, and first-degree block and left-axis deviation developed. Roentgenograms showed cardiac enlargement, pulmonary congestion and hydrothorax and coarse, mottled fibrotic streaking of the lungs. There was complete destruction of the distal phalanges, marked erosion of the middle phalanges and considerable deformity and narrowing of the phalangeal joint spaces. Esophageal studies suggested esophagitis and moderate cardiospasm, but were not characteristic of scleroderma.

The correlation of onset and exacerbation of illness, presumably early scleroderma, with emotional trauma is striking. Also, there was a definite history of thyrotoxicosis and thyroidectomy.

Case 7. M. M. (P.B.B.H. 103613), an Italian-born, 46-year-old housewife, was admitted to the hospital in 1938, with a 1-year history of limb pain, limitation of limb motion and intermittent leg swelling. For about 6 months increased sensitivity to cold had been present. There was increased skin pigmentation. Poor appetite and slight exertional dyspnea were also present.

Physical examination demonstrated heavy pigment, particularly over the face, back of the neck and forearms, and under the breasts. The skin of the forearms was dry. There was joint crepitus, restriction of left-shoulder motion and swelling of the finger joints. Leukoderma, tense, poorly resilient skin over the hands and feet, and immobility and absence of wrinkling of the face were noted. The patient was discharged to her family physician on January 22; no follow-up data were available.

The hemoglobin was 72 and 82 per cent; the red-cell count was 3,950,000 and 4,650,000. A stool was guaiac positive. The albumin-globulin ratio was 3.1:4.4.

There was a rapid onset of classic skin manifestations in this case. The albumin-globulin ratio was reversed within a year of onset.

Case 8. J. W. (P.B.B.H. D9360), a 34-year-old widowed Negress, was admitted to the hospital in April, 1945, because of recurring felons, cold sensitivity and abdominal wheals of 3 or 4 months' duration. The wheals were white, pruritic and surrounded by blue zones, and were complicated by secondary infections succeeded by scaling, desquamation, and depigmented scarring. She entered the hospital with a flexor tenosynovitis and osteomyelitis of the right index finger, which responded to surgical drainage and chemotherapy.

Examination of the blood showed a red-cell count of 3,300,000, with a hemoglobin of 11.8 gm. per 100 cc. The albumin-globulin ratio was 2.8:5.5. Roentgenograms revealed cardiac enlargement and dilatation of the left atrium and pulmonary artery suggestive of valvular disease. A skin biopsy was consistent with early scleroderma.

During the next few months, additional finger abscesses developed, and the cold sensitivity of the extremities increased. The initial symptoms of mild congestive heart failure began in July. Sudden severe dyspnea and episodic lumbar pain occurred 2 months later. Physical examination disclosed cool fingertips and toes; the skin over the dorsa of the hands and forearms was tight, patches of dark pigment were present on the cheeks, and there were Grade 2 apical and Grade 1 basal systolic precordial murmurs. Bronchopneumonia, responding to chemotherapy, occurred in September.

By early 1946, the congestive heart failure had responded to digitalization and a low-salt intake. Sympathectomy late in 1946 caused a remission of the Raynaud symptoms, but these recurred in March, 1947, accompanied by "rheumatoid" changes of the lower extremities, chills, fever, nausea, vomiting, dysphagia and pneumonitis. Some relief was obtained with salicylates. Roentgenograms indicated no esophageal abnormality. Cardiac enlargement and thickened pulmonary markings, particularly at the lung bases, were present in contrast to normal thoracic roentgenograms taken 5 months earlier. There was still slight anemia.

The patient steadily deteriorated, and was readmitted to the hospital in May, 1948, because of exertional dyspnea and pleural effusion, which responded to cardiac treatment. Electrocardiographic changes suggested cardiac ischemia.

Vaginal hemorrhage, epistaxis and phlebitis of the right lower leg occurred early in July, 1948. The circulation time was prolonged to 26 seconds; proteinuria was evident, but there was no longer a definite anemia.

The patient continued to do fairly well until September 8, when severe left-lower-quadrant pain, later shifting to the right upper quadrant, appeared. Physical examination 3 days later revealed tenderness in the right flank and right upper quadrant. She was discharged on September 20, but was bed ridden 1 month later with a recurrence of this pain, anorexia and arthritic pain. She died suddenly after an attack of paroxysmal nocturnal dyspnea 2 weeks later.

At post-mortem examination the cachectic cadaver exhibited small islands of normally pigmented skin on large areas of thick, white, shiny epidermis over the abdomen and dorsa of the hands. There were 390 cc. of clear peritoneal fluid, many thin, white pleural and thick pericardial adhesions, and 2 white, firm masses, probably thymic, were located in the anterior superior mediastinum; each weighed 65 to 70 gm. and contained soft red and pink lobular tissue.

The heart, which weighed 480 gm., presented a 3-cm. depression of the left ventricle, dilatation of the right ventricle, hypertrophy of the left ventricular papillary muscles and mitral-valve thickening, especially along the diffusely nodular margins. There was striking tricuspid nodularity.

Microscopical examination showed much of the epicardium and surrounding fat to be replaced by connective tissue. There was diffuse myocardial fibrosis, most prominent in the perivascular areas. Increased collagen was noted in the cardiac valves and endocardium. There was marked medial and intimal thickening of myocardial arterioles and capillaries, some of the former showing complete obliteration of the lumens.

There was focal pleural fibrosis, some increase in alveolar and peribronchial connective tissue, pulmonary congestion and edema, many pigment-laden macrophages and pulmonary arterial thickening. The thymic stroma was composed of dense collagen. There was variable increase of dense, abundant, submucous collagen of the tongue and esophagus and a portion of the ileum. Most renal glomeruli had thickened Bowman membranes and capillaries, and there were occasional necrotic glomerular capillary loops. Variable thickening and hyalinization of the renal arteriolar wall were present. The meningeal and perineural arterioles exhibited medial and intimal hyperplasia. Few mammillary ducts or acini were noted, the breast fat being largely replaced by collagen. The dermal collagen was greatly increased, with shallow dermal papillae and squamous atrophy.

The principal pathological diagnoses were generalized scleroderma, inflammation of the mitral and tricuspid valves, arteriolar sclerosis and pulmonary congestion.

The wheals, felons and pruritic lesions occurring early in the course of the illness were unusual. The recurrent pulmonary symptoms and the three and a half years of total illness were most striking.

Case 9. I. K. (P.B.B.H. D8695), a 41-year-old housewife, began to have weakness, fatigue, left-sided facial swelling, and pain and paresthesias over the wrists late in 1944. Within 1 year, the fatigue was worse, and generalized stiffness, fever, anorexia, joint pain and swelling, and cold, cyanotic digits were present. In November, 1945, numbness and shooting pains appeared over the right side of the face, the left becoming similarly involved by the date of admission to the hospital in January, 1946. By that time, the skin of the hands had become shiny and tightly drawn. Physical findings included hypersensitivity

of the right 5th nerve, scattered joint stiffness and swelling, nodules over the fingers and elbows and a Grade 1 pulmonic systolic precordial murmur; the skin over the face and hands was glossy and drawn. The temperature was 100°F. Rheumatoid arthritis and "collagen disease" were the diagnoses.

There were remissions, but the general course of the illness was downward, despite testosterone, penicillin, nicotinic acid, salicylates, iron and spray radiation therapy. By July the skin changes over the extremities had progressed to the tight, pigmented, shiny appearance characteristic of scleroderma, and there were Grade 3 apical and Grade 2 basal systolic precordial murmurs. The urine gave a + test for protein. The sedimentation rate was 2.5 mm. per minute. Examination of the blood showed a red-cell count of 4,000,000, with a hemoglobin of 9.1 gm. per 100 cc. and a hematocrit of 21 per cent. Roentgenograms revealed triangular cardiac enlargement, pulmonary congestion, right basal atelectasis and moderate esophageal dilatation, with constriction of the lower esophagus. An electrocardiogram demonstrated abnormal ventricular complexes and premature ventricular beats.

Substernal oppression, hoarseness, pulmonary basal fibrosis and a transient macular eruption of the face and upper part of the trunk developed within the next 4 months. The blood pressure was elevated to 160/90 in November. The illness continued to progress, palpitation, dyspnea and orthopnea appearing by April, 1947. There were also dry, crackling rales bilaterally. During the 7th hospital admission, 5 months later, a sudden pain in the anterior portion of the chest, relieved by Demerol, and a Grade 3 pleuropericardial friction rub developed, succeeded by a gallop rhythm, tachycardia and an occasional extrasystole. After these findings had subsided, the friction rub recurred, accompanied by dyspnea, splenomegaly and hepatomegaly.

By January, 1948, left-upper-quadrant pain and substernal aching were present. Two months later, transient hoarseness developed, and the patient was troubled by postprandial pain in the right upper quadrant, nausea and vomiting. The albumin-globulin ratio was still normal and continued so until death. She was placed on a modified antiulcer regimen. Stilbestrol, liver, bistimate, A. T. 10, Benadryl and ergostanyl acetate had given no definite benefit. There was no anemia at this time. A chronic, nonproductive cough, pain in the right anterior part of the chest aggravated by respiration, extrasystoles and ankle edema developed within the next 3 months. Also, there was urgency to defecate, but without results. The patient was almost completely bed ridden by this time. Repeated skin biopsies had long since confirmed the diagnosis of scleroderma.

The last admission was in January, 1949, with new complaints of abdominal distention, epigastric burning and raising of much frothy, white sputum. Two weeks after entry, the temperature spiked to 102.4°F. Tachycardia and tachypnea developed, the extremities became cold, and the blood pressure was unobtainable. Pulmonary rales, an elevated white-cell count, extrasystoles, a faint gallop rhythm, vomiting and aerophagia appeared within a day, and the patient died on January 17.

Autopsy showed the body of an emaciated woman, who appeared aged; the pleural and pericardial cavities were obliterated by dense, white adhesions, and there was 600 cc. of clear fluid in the peritoneal cavity.

The heart, which weighed 400 gm., had pale, firm myocardial tissue. The base of the left lower pulmonary lobe was gray and solid. Stiffness of the tongue was noted, the oropharyngeal mucosa was gray, thickened and leathery, and firm, white, thickened plaques were present within the esophageal and intestinal walls. The proximal 30 cm. of small intestine was markedly dilated, the remainder of the intestine showing segmental dilatation. There was purplish discoloration of the proximal 20 cm. of bowel. The renal cortexes were coarsely granular, and there were 0.1-cm. hyaline areas in the renal medullae.

Microscopical examination demonstrated irregular collagenous thickening of the pericardium, foci of myocardial fibrosis containing viable myocardium, and thickening of the mitral-valve surface by fibrillary collagen at the attachment of the chordae tendineae. Moderate myocardial fibrous arterial and arteriolar thickening was evident. There was irregular collagenous thickening of the aortic adventitia, the small adventitial arteries exhibiting marked intimal thickening, and some containing organized thrombi. Focal intimal thickening of the aorta by hyalinized fibrous tissue was observed. There was much fibrosis of the tracheal submucosa and surrounding cartilaginous plates. Scattered pleural and intra-alveolar pulmonary fibrosis, right-lobar-pneumonia changes, and pulmonary vascular thickening were evident. The spleen showed marked capsular fibrotic thickening, arterial-wall thickening and onion-skin appearance of the arterioles.

There was submucosal and muscular fibrosis of the tongue, posterior pharynx, esophagus and appendix. Segmental thinning of the ileal and jejunal walls in areas of dilatation and muscular atrophy accompanied focal intestinal fibrosis and arterial-wall thickening. There was considerable central lobular hepatic fibrosis. Small areas of renal cortical fibrosis and arterial-wall thickening were noted. Considerable thyroid fibrosis was evident. There were a few small acini, and ducts persisted in dense breast fibrous tissue. Increased fibrous tissue was present in the skeletal muscle, particularly the psoas. The corium of the skin was greatly thickened and fibrotic.

The principal pathological diagnoses were scleroderma, generalized, and congestive heart failure.

Facial swelling was a unique initial symptom. Death occurred in five years.

CASE 10. L. C. (P.B.B.H. 8A629), a 43-year-old, foundry vice-president, was admitted to the hospital in July, 1948, because of dull, aching shoulder pain on motion that had first been noted early in 1947 and had quickly progressed to exertional metatarsophalangeal pain and generalized joint swelling. The sedimentation rate and eosinophil count were elevated. Remissions occurred, but by 1948, despite gold therapy, rest and penicillin, disability was so severe that the patient was unable to work. Other complaints included epigastric distress and blurring of the right ocular vision for several months, loss of strength in both hands, thickening, mottling and blueness of the skin over the hands and feet for 2 or 3 months, and hoarseness for 1 month. A tender nodule, 1 by 2 cm., had appeared in the left Achilles tendon.

Physical examination showed the skin over the fingers to be shiny, mottled and thickened, with depressed scars. There was hyperpigmentation and cold cyanosis of the hands, slight joint swelling, a nodule in the left Achilles tendon and a Grade 1 apical systolic precordial murmur. Scleroderma with Raynaud's syndrome was diagnosed. Roentgenograms demonstrated minimal osteoporosis and hypertrophic changes. The basal metabolic rate was + 19 per cent, and the albumin-globulin ratio 4.6:1.8.

Sympathectomy, chrysotherapy and aspirin therapy induced some remission, but by early 1950 dysphagia and flexion deformity of all fingers had developed, the systolic apical murmur was Grade 2, and skin biopsy was consistent with scleroderma. The blood pressure was 170/80 at this time. Cortisone therapy, 75 mg. a day, afforded relief and has been continued for 3 years with considerable symptomatic improvement.

Roentgenograms showed the esophagus to be slow to empty and moderately dilated, with poor peristalsis, and a slight supradiaphragmatic constriction was evident by September, 1950. Chest films revealed left-sided cardiac enlargement, but an electrocardiogram was normal.

This male patient demonstrated early Raynaud syndrome and severe arthritic symptoms.

CASE 11. J. M. (P.B.B.H. 1D233), a 41-year-old female textile worker, was admitted to the hospital in June, 1949, because of epidermal redness and pruritus beneath the right ear, soreness over the zygoma, orthopnea, anorexia, atypical dysphagia, slight dyspnea and vague abdominal pains of 1 or 2 years' duration. Scattered, blotchy brown pigmentation of the trunk, extremities and neck was prominent by November, 1948. Fatigue and Raynaud's symptoms of the shiny, tense fingers were also present by this time.

Hyperthyroidism was successfully treated by subtotal thyroidectomy 22 years before entry. "Kidney disease" of 10 to 12 years' duration had supposedly begun 16 years before admission, after the 9th month of pregnancy.

Physical examination demonstrated an asthenic woman with mask-like facies, scattered dark-brown discoloration of the neck, trunk and extremity pigmentation, thickening and tenseness of the skin over the hands, forearms and face, 3 scars in the anterior part of the neck and slight thyroid enlargement. Aside from an occasional + test for protein, the laboratory and radiologic studies were within normal limits. A skin biopsy confirmed scleroderma.

Steady deterioration continued over the following 6 months, despite administration of para-aminobenzoic acid, testosterone and ACTH. Physical examination early in 1950 revealed, additionally, shiny, waxy, thickened, nonelastic skin over the anterior tibias and stiffness and decreased motion of the joints. Electrocardiograms showed transient, nonspecific, abnormal changes.

The patient was readmitted to the hospital in September with a "chest cold" and a recent history of sharp, postprandial epigastric pain, nausea and vomiting, mild diarrhea, weakness and dizziness. There was a Grade 1 soft systolic apical precordial murmur. Roentgenograms showed the esophagus to be hypotonic, with absence of peristalsis in its lower third. A stool gave a + guaiac reaction.

Soreness over the zygoma was an initial symptom in this case. There was a history of hyperthyroidism and thyroidectomy.

CASE 12. M. R. L. (P.B.B.H. 3970) a 35-year-old housewife, entered the hospital in March, 1942, with a history of skin-color change in the cold dating back to the age of 19, immediately after the birth of her first child. The hands especially were involved, numbness and pain on cold developing later. Tightness of the skin was noted by her physician when she was 23. A thyroidectomy, to "improve the circulation," was performed 4 or 5 years later, and the patient was placed on thyroid medication. Dysphagia, progressing to esophageal stricture, constipation, "gas" pain in the lower chest, and hypomenorrhea developed during the following 8 years. Sympathectomy was performed in 1941.

Physical examination showed the skin to be hard, puffy and shiny, particularly over the hands and fingers. The sedimentation rate was 28 mm. per hour; the hematocrit was 36 per cent. The basal metabolic rate was −22 per cent. An electrocardiogram demonstrated abnormal ventricular complexes with a low electromotive force. Roentgenograms revealed loss of terminal phalangeal bone substance, slight diffuse pulmonary streaking, triangular cardiac enlargement, with diminished amplitude of pulsations, and esophageal dilatation, with supradiaphragmatic narrowing. The diagnosis was generalized scleroderma.

By December the patient was losing weight, upper epigastric and right sternal pain accompanied meals, there was diarrhea and constipation, and only alternate pulse beats were palpable. An electrocardiogram again revealed premature ventricular beats.

Raynaud's phenomenon, which was the earliest manifestation of this illness, began immediately after the patient's first delivery. Thyroidectomy again appears in the history of a case of typical scleroderma, but there was no definitive diagnosis of thyrotoxicosis. The duration of scleroderma was probably between thirteen and seventeen years when the patient was last examined in December, 1942, multiple system involvement having been present for at least eight or nine years.

CASE 13. R. W. (P.B.B.H. 8C9), a 36-year-old Negress, entered the hospital in September, 1950, with a 3-year history of vitiligo involving the cheeks, fingertips and upper chest, and weight loss of 14 pounds. Stiffness and swelling of the right finger joints began about 1 year later and quickly spread to the left hand, accompanied by some limitation of shoulder motion. Despite temporary remission, skin and joint disability became progressively worse, with weakness, fatigue, slight ankle edema and severe dysphagia; Raynaud-like attacks of finger numbness were present by the date of entry.

Physical examination revealed vitiligo scattered over the face, neck and hands, thickened, tight skin, limitation of joint motion and a Grade 2 apical systolic precordial murmur. Roentgenograms showed some delay in passage of barium through the esophagus and blunting of the right costophrenic angle, with elevation and adhesion of the lateral right leaf of the diaphragm. A skin biopsy was consistent with scleroderma. An electrocardiogram and laboratory data were within normal limits.

Therapy, including a low-salt diet, ascorbic acid, right-stellate-ganglion block, physical therapy and a 3-week course of ACTH, brought some improvement.

Vitiligo was especially striking in this case. The Raynaud symptoms and the skin and joint changes were not regarded as significant by the patient, and it was the weight loss that caused her to enter the hospital.

CASE 14. M. F. (P.B.B.H. 7B598), a 37-year-old Italian-born housewife, was admitted to the hospital in October, 1950, with a history of a heart murmur and frequent epistaxes after diphtheria in early childhood. She had been married for 10 years, and had never succeeded in becoming pregnant. Pain, stiffness, swelling, and warmth of the proximal interphalangeal joints had begun 3 years before admission. Generalized joint involvement, periarticular nodules, skin hyperpigmentation and thickening over the joints and face, as well as a malar skin eruption, developed within a few weeks. Forty pounds were lost in this 3-year interval. Difficulty in opening the mouth, orthopnea, gingival pain, increasingly severe hoarseness and a "chest cold" progressing to night sweats, fever and a productive cough appeared within the year preceding entry.

Physical examination revealed malar telangiectasia, swollen, red, hot, stiff joints, thickened, taut, hyperpigmented skin over portions of the trunk and extremities, and vitiligo over the proximal interphalangeal joints. There were soft, cystic, 3-cm. masses on the wrists, and firm subcutaneous nodules were scattered over the extremities. Thoracic auscultation demonstrated dullness, bilateral rales and a Grade 4 apical systolic precordial murmur. Roentgenograms showed right-sided and left-sided cardiac enlargement suggestive of combined valvular disease, pulmonary congestion, atelectasis and pneumonitis of the right base, joint-space narrowing with associated soft-tissue swelling of the hands, destruction of the interphalangeal joints of the thumbs with marked posterior dislocation of the distal phalanx of the left thumb and slight demineralization of the bones of the hands. A later esophageal examination, in contrast to the negative first one, revealed diminished peristalsis, delay in emptying and minimal dilatation, all compatible with scleroderma.

Examination of the urine showed intermittent + tests for protein. Examination of the blood disclosed a hemoglobin of 8.5 gm. per 100 cc., a hematocrit of 27 per cent and eosinopenia (counts of 6 to 23 per cubic millimeter). The albumin-globulin ratio was 2.5:3.4 and 2.3:4.8, and the vital capacity was reduced to 1200 cc. Treatment included blood transfusion, ascorbic acid, potassium iodide, antibiotics, iron, testosterone and ACTH therapy for over 1 month, with a marked, but temporary, remission during hospitalization.

Despite vitamin D, prostigmine, quinidine, morphine, ammonium chloride and a moderately successful course of cortisone therapy, the patient's downhill course continued, dyspnea and anorexia being evident by January, 1951. Lobar pneumonia at this time responded to penicillin therapy, and auricular flutter was abruptly terminated by digitalization.

Recurrent pulmonary infections are not uncommon with sclerodermatous pulmonary fibrosis. This patient exhibited severe hoarseness, a finding not uncommon in scleroderma (and also present in Cases 9 and 10). The telangiectasia over the malar areas was unique in this series of cases. Proteinuria, fever, anemia and early arthralgia were other findings suggestive of acute disseminated lupus erythematosus. The simultaneous occurrence of clinical features of both diseases in this case suggests a closer relation between disseminated lupus erythematosus and scleroderma than that usually apparent.

CASE 15. G. F. (P.B.B.H. 0D829), a 43-year-old single clerk, entered the hospital in November, 1949, with shortness of breath as his chief complaint. Four years earlier, a single transient episode of early-morning numbness of the hands had occurred.

This reappeared 10 months before admission and was accompanied by finger paresthesias. Definite stiffness of the hands and evanescent knee and shoulder stiffness began 4 months later. Dry, scaling, psoriasiform eruptions of the hands and elbows, later spreading to the lower extremities and ear lobes, appeared at this time. One month later (around June, 1949) exertional dyspnea and cough productive of white sputum developed. The dyspnea steadily worsened, tachypnea at rest being evident within 3 months. Ten pounds had been lost in the 10 months before admission.

Physical examination showed a dry, scaly, shiny skin eruption involving the hands and ear tips, psoriatic plaques over the elbows, stiffness of the hands and shoulders and fusiform swellings involving the first interphalangeal and metacarpophalangeal joints; the skin of the fingers was shiny and indurated. Rib cage and diaphragmatic movements were diminished. There were dry basal pulmonary rales, and a Grade 2 pulmonic systolic precordial murmur was present.

Roentgenograms revealed coarse basal mottling of the lungs, cardiac enlargement to the left and decalcification and soft-tissue swelling of the affected joints. An electrocardiogram disclosed incomplete right-bundle-branch block. Laboratory studies were within normal limits. The albumin-globulin ratio was 2.7:2.2.

During the hospital stay, dyspnea and cough continued. A maximum temperature of 101°F. appeared irregularly. Penicillin was of no benefit.

The patient was readmitted to the hospital 2 years later. Dyspnea had steadily increased. Cortisone, 25 mg. daily by mouth, had been taken over the previous 6 months, with slight improvement of the joint symptoms and of the psoriasis. Physical examination demonstrated clubbing of the fingers, smooth prominence of the skin over the olecranon processes, distention of the neck veins, hepatosplenomegaly, a protodiastolic gallop cardiac rhythm and frequent cardiac extrasystoles. The corrected sedimentation rate was 16 mm. per hour.

Radiologic studies showed diminished pulmonary aeration and calcific deposits in the distal flexor aspect of each thumb. Electrocardiograms revealed auricular flutter, multifocal repetitive premature beats and changes suggestive of a posterior myocardial infarction.

ACTH therapy was instituted, but was quickly discontinued because of apparent aggravation of the cardiac arrhythmias. A high-protein, low-salt diet, procaine amide and para-aminobenzoic acid therapy were instituted.

One month after discharge, the patient was readmitted to the hospital with increasing fatigue, dyspnea, ankle edema and weight gain of 13 pounds despite institution of digitalis, Mercuhydrin and ammonium chloride therapy. Quinidine had not affected the cardiac arrhythmias. Additional physical findings included a totally irregular cardiac rhythm, diminished pulmonary resonance, hepatic tenderness, ++ pitting ankle edema and breast enlargement. The circulation time was 45 seconds (heart-to-tongue method); the venous pressure was equivalent to 290 mm. of water, and the vital capacity was 1400 cc. compared with values 2 years earlier of 9 seconds, 100 mm. and 2000 cc. respectively. Chest films also suggested pulmonary congestion. The electrocardiographic changes, suggestive of transmural scarring, and the cardiac arrhythmias persisted.

Despite Mercuhydrin and digitoxin therapy, the patient suddenly collapsed on the 3d hospital day. His heart sounds were inaudible, and respiration ceased a few seconds later.

At post-mortem examination the pericardial sac was much enlarged and contained 800 cc. of serous fluid. The moderately enlarged heart (weighing 490 gm.) showed severe myocardial fibrosis of the left ventricle, with firm, white, uniformly distributed patches, 2 or 3 cm. in diameter, and marked dense, white pulmonary fibrosis. The spleen was enlarged, weighing 650 gm., and exhibited prominent follicles; generalized lymphadenopathy was present.

Microscopical examination showed extensive interstitial, perivascular and subendocardial ventricular and atrial fibrosis. Considerable intimal proliferation of the smaller arteries and arterioles was present, with zones of arteriolar sclerosis corresponding to the areas of fibrosis. A similar correlation was observed in the lungs, some areas of fibrosis entirely obliterating the pulmonary parenchyma or encircling cyst-like zones (Fig. 7).

Changes typical of arteriolar sclerosis and intimal proliferation were evident also in the stomach, colon, mesentery and shoulder-joint capsule. Intimal proliferation of the larger renal arteries was present. Moderate fibrosis was noted in the esophagus, stomach and breast. A great increase in dermal collagen, associated with atrophy of the dermal appendages, was observed. There were also hepatic chronic passive congestion and generalized lymphoid hyperplasia.

The chief pathological diagnoses were generalized scleroderma and arteriolar sclerosis.

This case exhibited slow, overt development of sclerodermatous skin lesions, and rapid, fatal progression of cardiorespiratory lesions. All forms of therapy attempted for the latter were of no avail. It is noteworthy that this case and Case 1 both exhibited aggravation of serious cardiac arrhythmias by cortisone and ACTH therapy to the extent that discontinuance of these agents was required. The correlation of fibrosis and vascular changes of sclerosis and intimal hyperplasia was quite striking in this case.

Summary

Fifteen cases of scleroderma are described and analyzed. It is proposed that the term progressive systemic sclerosis more accurately reflects the diffuse nature of the disease. All patients had skin lesions, and 14 exhibited multiple system involvement, including the cardiorespiratory system and the gastrointestinal tract, as well as constitutional changes.

Roentgenograms were studied in 9 cases. Common findings included pulmonary fibrotic streaks and nodules, cardiac changes and esophageal abnormalities. Soft-tissue, bone, and joint lesions were frequent. Four patients had calcinosis.

Electrocardiographic changes were frequent and variable. Arrhythmias were the most prominent aberration.

All autopsied cases demonstrated diffuse visceral fibrotic lesions. Vascular sclerosis and intimal hyperplasia were common. One case displayed inflammation of the mitral and tricuspid valves.

All forms of therapy, including ACTH and cortisone in most cases, proved ineffective.

A new hypothesis regarding the relation of this entity to other so-called collagen diseases is offered.

We are indebted to Drs. Clinton V. Z. Hawn, Samuel Hicks, Robert Linn and George W. Thorn for their helpful advice and criticism.

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FAMILY OUTBREAKS OF INFECTIOUS HEPATITIS*

Prophylactic Use of Gamma Globulin

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BOSTON

ALTHOUGH the epidemiology of infectious hepatitis has been extensively studied in institutional outbreaks,[1-7] the incidence and mode of transmission of the disease in families in civilian life has received scant attention. Pickles,[8] Propert,[9] Newman[10] and Kunkel[11] have reported outbreaks among members of single families and their immediate contacts. Ford,[12] in a study involving 300 cases in a civilian epidemic, found that 17 per cent of the households had multiple cases of infectious hepatitis.

Stokes and Neefe[13] first demonstrated the value of gamma globulin prepared from pooled human plasma in the prevention or modification of infectious hepatitis in a group of persons exposed in a severe outbreak of the disease in a summer camp. The effectiveness of gamma globulin was subsequently confirmed in epidemics involving the inmates of a mental institution[14] and large numbers of military personnel in World War II.[15] Recently, Stokes[16] suggested that as little as 0.01 cc. of gamma globulin per pound of body weight may be protective against infectious hepatitis.

Sporadic cases of infectious hepatitis in the greater Boston area have provided an opportunity to study the incidence of multiple cases occurring within families and to determine the value of gamma globulin in the control of household contacts.

METHODS AND MATERIALS

All the patients included in this study were initially seen either in the Pediatrics Clinic of the Children's Medical Center or of the Beth Israel Hospital, Boston, or, in a few cases, in the private offices of members of the staff of these hospitals. In either event, the diagnosis of infectious hepatitis was made on the basis of a history of malaise, anorexia, vomiting, fever, abdominal pain, dark urine, light stools, icterus of the skin and scleras and an enlarged, tender liver. Liver-function tests including cephalin-cholesterol flocculation,[17] thymol turbidity,[18] thymol flocculation,[19] one-minute serum bilirubin[20, 21] and total serum bilirubin[20, 21] were all positive when each patient was first seen. In addition to these tests, increased bile and urobilinogen in the urine were demonstrated in most cases, and infectious mononucleosis was ruled out by blood smears and heterophil-antibody agglutination. None of the patients had received injections or transfusions within six months of the onset of symptoms.

The family contacts of the patients were divided into two groups without selection. The decision whether or not to give gamma globulin was made solely on the basis of the availability of the material at the time the original case was first seen. Gamma globulin was given to all the immediate members of 17 families and to none of the remaining 29 families that served as controls. Although the recommended dose was 0.1 cc. of gamma globulin

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per pound of body weight, with a maximum of 5 cc. in infants and children and 10 cc. in adults, a few persons received less (0.01 to 0.06 cc. per pound of body weight) because of scarcity of the material.

All the families in both the treated and untreated groups were studied three months to a year after the initial illness. The diagnosis of hepatitis in other members of the families was based solely on the occurrence of clinical jaundice; no attempt was made to diagnose subclinical infections.

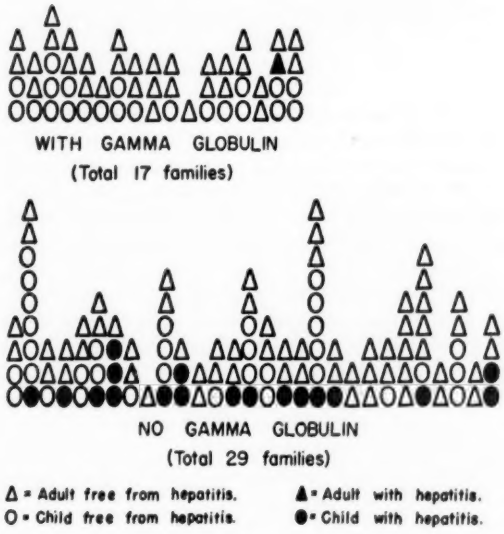
WITH GAMMA GLOBULIN
(Total 17 families)
NO GAMMA GLOBULIN
(Total 29 families)
Δ = Adult free from hepatitis.
▲ = Adult with hepatitis.
O = Child free from hepatitis.
● = Child with hepatitis.

FIGURE 1. *Incidence of Secondary Cases in Families Followed after the Initial Case of Hepatitis Was Diagnosed.*

All patients below fifteen years of age were classified as children, and all others as adults. The patient with hepatitis in the gamma-globulin group contracted the disease two days after receiving the material.

RESULTS

A total of 64 patients with hepatitis from 46 families were observed in this study. The occurrence of secondary cases in families followed after the initial case of hepatitis was diagnosed is shown in Figure 1. All those below fifteen years of age were classified as children, and all others as adults.

TABLE 1. *Incidence of Reinfection within Families.*

GROUP	PERSONS NOT RECEIVING GAMMA GLOBULIN	PERSONS RECEIVING GAMMA GLOBULIN
Families without further cases	15 (52%)	16 (94%)
Families with additional cases	14 (48%)	1* (6%)
Families with 1 additional case	11 (40%)	
Families with 2 additional cases	2 (5%)	
Families with 3 additional cases	1 (3%)	
Totals	29	17

*Hepatitis developed 2 days after administration of gamma globulin.

The data summarized in Table 1 show that additional cases of hepatitis developed in 48 per cent of the families not treated with gamma globulin, whereas the disease appeared in only 1 person among the family contacts treated with the material. This occurred in a patient who manifested jaundice only two days after the gamma globulin had been given. In the untreated group, 2 additional cases appeared in each of 2 families, and in 1 of the families there were 3 additional cases. Gamma globulin was given to 4 of the previously untreated families after the appearance of a second case, and no subsequent cases of hepatitis were observed.

TABLE 2. *Incidence of Hepatitis Infection among Exposed Adults and Children within the Families Treated with Gamma Globulin and Those Not Treated.*

GROUP	PERSONS NOT TREATED WITH GAMMA GLOBULIN		PERSONS TREATED WITH GAMMA GLOBULIN	
	NO. EXPOSED	NO. WITH HEPATITIS	NO. EXPOSED	NO. WITH HEPATITIS
Patients over 15	63	0	33	1* (3%)
Children under 15	51	18 (35%)	22	0
Totals	114	18 (16%)	55	1* (2%)

*Hepatitis developed 2 days after administration of gamma globulin.

The incidence of hepatitis among the exposed adults and children is summarized in Table 2. It was found that in the untreated group, 18 out of 51 exposed children (35 per cent) contracted hepatitis, whereas none of the 22 children treated with gamma globulin subsequently gave clinical evidence of hepatitis.

DISCUSSION

From this study it is obvious, first, that the exposure of children to hepatitis within family groups results in surprisingly high incidence of the disease, secondly, that gamma globulin is extremely effective in preventing the disease and, thirdly, that the adults involved in these outbreaks appear to have a relatively high degree of immunity.

On questioning of the parents, it soon became apparent that isolation technics were unsatisfactory and impractical within the average home. When there were other children in the house, it proved to be almost impossible to prevent intimate contact between the patient and other children. Separate dishes and silverware were often accidentally mixed with those used by the rest of the family. In only one household was it possible for the patient to have a separate bathroom. In all others, the patient either used the same toilet as other members of the family, or used a bedpan. The stools from the bedpan were invariably emptied into the same toilet used by the rest of the family.

It appears that prophylaxis with gamma globulin is the only effective method known of preventing the spread of infectious hepatitis through family groups. The present study indicates that it is as useful in civilian life as in institutional and military outbreaks.[14, 15] It must be given early and at least five to seven days before the onset of jaundice to

be effective.[15] In the 1 patient in this series who contracted hepatitis despite gamma-globulin prophylaxis, jaundice appeared two days after the material had been given. The proper dosage remains to be determined. It is probable that the dosage based on 0.1 cc. of gamma globulin per pound of body weight originally recommended is too high.[15] The dose of 0.01 cc. of gamma globulin per pound suggested by Stokes[16] failed to prevent the disease in 1 or 2 cases during an outbreak, but did appear to be effective in preventing the spread of hepatitis. With the impending shortage of gamma globulin, we believe that the smallest dose should be used that can be proved to be effective in controlling the spread of the disease within families if given early. Further studies in progress suggest that 0.01 cc. of gamma globulin per pound of body weight is highly effective.

Whether every child exposed to infectious hepatitis within a family group should be given gamma globulin remains to be determined. In recent years, increasing evidence has accumulated that infectious hepatitis in childhood is not necessarily a benign disease. Hsia[22] has found 4 children with chronic hepatitis and cirrhosis in a follow-up study of 30 children with infectious hepatitis. Drake[23] has reported the development of cirrhosis and ascites in 2 children after apparently complete recovery from infectious hepatitis. On the other hand, the condition appears to be relatively more benign in children than in adults, and complete prevention of the disease during childhood may be unwise. Stokes[15, 16] and Drake[23] have suggested that the disease may be prevented by administration of gamma globulin but that a mild inapparent infection may confer lasting immunity very much as modified measles does: However, this may only be true of children in institutions where the disease is endemic and exposure to the virus is constant so that infection may occur as the passive immunity conferred by gamma globulin wanes. There is obviously need for further studies on gamma-globulin dosage in this disease to determine the extent to which small doses will permit the development of modified hepatitis.

Gamma globulin is definitely indicated in sick children exposed to hepatitis. This is especially true of children who are debilitated by chronic digestive and nutritional disturbances. In all other cases the material may be given at the discretion of the attending physician with the knowledge that it will be effective in preventing the spread of the disease within the family. Only future work on the long-term effects of infectious hepatitis in children may determine whether or not the disease should be prevented in childhood.

Although Stokes[24] concludes that 35 per cent of adults are immune to infectious hepatitis and only 1 of the exposed adults in this study contracted the disease, administration of gamma globulin to the adult members of families in which a case has occurred may be justified on the grounds that the disease is potentially a dangerous one in adult life. This might be particularly true for young adults (under thirty years of age), pregnant women or adults with chronic illnesses. Skin testing with attenuated or inactivated virus may permit the selection of susceptible adults in the future and may thus eliminate the waste of gamma globulin that results from indiscriminate use.

Summary

In 46 families in which an initial sporadic case of infectious hepatitis was observed the incidence of secondary cases of the disease was studied.

In 17 of these families, gamma globulin was administered to the other members of the household. Only 1 case of infectious hepatitis developed among 33 adults and 22 children so treated; in this case jaundice was noted two days after the injection.

In the 29 remaining families, no gamma globulin was administered to the contacts. Secondary cases appeared in 14 (48 per cent) of these families. Among 63 exposed adults, none contracted the disease, but frank jaundice developed in 18 out of 51 (35 per cent) exposed children.

The dosage of gamma globulin and indications for its use in the prevention of infectious hepatitis in family medical practice are discussed.

Since this paper was submitted for publication 35 additional families with an initial sporadic case of infectious hepatitis have been studied. Additional cases of infectious hepatitis with jaundice developed in 32 per cent of the families in this group. None of the patients with secondary cases had received gamma globulin.

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THE GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH ACUTE HEPATITIS*

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THE Gullain-Barré syndrome is an acute disorder of the peripheral nervous system manifested primarily by paralysis but frequently including sensory loss as well. There is often a history of an antecedent infection, usually from a nonspecific disease of the upper respiratory tract. Occasionally, the syndrome follows a specific disease, usually infectious mononucleosis.[1] Acute hepatitis is rarely a complication. There are only 4 previous cases in the literature of such an association.[1-4]

CASE REPORT

A 42-year-old male patient was well until 10 days before admission to the hospital, when he noted anorexia and dark urine. He had no knowledge of exposure to persons with jaundice, but had received immunizing injections 34 days earlier. Seven days before admission, the legs became weak and felt as if they were "asleep." On the next day the weakness increased and was accompanied by pain in the legs, forearms and hands. Three days before admission he was barely able to walk, and was admitted to another hospital, where diffuse weakness of all extremities was noted. The tendon reflexes were absent in the legs, but sensation was normal. The spinal fluid showed a normal cell count and a protein concentration of 93 mg. per 100 cc. On the day before admission to this hospital there was numbness of the right cheek, and on the day of admission, weakness of the facial muscles appeared. Definite jaundice was also present.

Physical examination demonstrated jaundice of the scleras and skin, although the liver edge was neither palpable nor tender. The patient could not stand without support, and the finger-to-nose and heel-to-shin tests were performed poorly. There was generalized weakness of all muscles of the extremities but careful testing revealed no complete paralyses. There was bilateral facial weakness. Rectal sphincter tone was very poor. No superficial or tendon reflexes could be elicited. Sensory examination demonstrated the loss of position sense in the feet.

Laboratory data disclosed a serum bilirubin concentration of 4.1 mg. per 100 cc. The thymol turbidity and cephalin flocculation were elevated. The blood hemoglobin concentration, red-cell count, white-cell count, differential count and sedimentation rate were normal. The heterophil-antibody agglutination on admission and throughout the course of the disease was positive only in a dilution of 1:7. The spinal fluid was normal except for a protein concentration of 99 mg. per 100 cc.

There was no change in the patient's condition during the first 3 hospital days, although there was incontinence of feces on the 2d day. On the 3rd day treatment with ACTH (adrenocorticotrophin) was begun. A daily intravenous infusion of 5 per cent dextrose containing 25 mg. of ACTH was given over a period of 8 hours. On the 4th day definite improvement was noted in both the neurologic and the hepatic disorders. By the 7th day the facial weakness had almost disappeared. On the 13th day the serum bilirubin concentration was normal. ACTH was stopped after the 15th day. Thereafter the neurologic disease continued to improve, but the jaundice reappeared and the serum bilirubin concentration reached 8.3 mg. per 100 cc. on the 23d day. The liver edge was first palpable at this time 6 cm. below the costal margin. ACTH was resumed for the next 14 days. By the 29th day position sense had returned, and by the 40th day the patient could stand alone. The tendon reflexes were still absent. Both the serum bilirubin concentration and the bromsulfalein excretion were normal at this time.

Thereafter, he received intensive physical therapy and showed a rapid gain in strength. On the 67d day the spinal-fluid protein concentration was 57 mg. per 100 cc. Although there were no symptoms of hepatitis, the liver edge was still felt 7 cm. below the costal margin, and the bromsulfalein retention had increased to 11 per cent. Complete muscle evaluation on the 108th day showed normal strength throughout. Biceps jerks had then returned, but there was still some inco-ordination of fine movements of the hands. At this time the liver edge was still palpable, but the retention of bromsulfalein dye had fallen to 7 per cent. Knee jerks were first observed on the 134th day, when motor co-ordination was completely normal. By the 200th day, the ankle jerks had returned. The spinal-fluid protein concentration was 35 mg. per 100 cc. The liver was no longer palpable and all liver-function tests, including the bromsulfalein excretion, were negative. The effect of ACTH is shown in Figure 1.

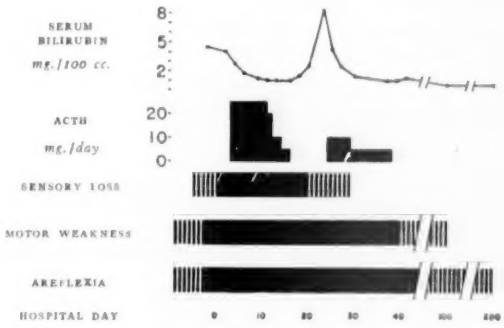

FIGURE 1. *Effect of ACTH on Acute Hepatitis Associated with the Guillain–Barré Syndrome.*

Three needle biopsies of the liver were performed during the patient's illness. The 1st, obtained on the 11th day, showed some necrosis of the liver cells, moderate diffuse inflammation in the lobules, with a tendency to focalization, and moderate infiltration of the portal areas. The pathological interpretation was moderate acute hepatitis. The 2d biopsy, on the 103d day, revealed a few scattered foci of necrosis in the lobules and slight cellular infiltration of the portal areas, indicating mild active hepatitis. The 3d biopsy, on the 200th hospital day, showed similar but even milder histologic changes.

DISCUSSION

This case presents typical clinical and laboratory features of the Guillain–Barré syndrome, as well as typical clinical, laboratory and histologic findings

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of acute hepatitis. Visceral lesions have been found occasionally in patients with Guillain–Barré syndrome. In 3 autopsied cases, Sabin and Aring[5] described histologic lesions in the liver consisting of small foci of necrosis and cellular infiltration in the lobules, and cellular infiltrations in the portal spaces. There were similar minor changes in other viscera. In the series of 50 autopsied cases presented by Haymaker and Kernohan[1] 1 showed cirrhosis of the liver, thought to be unrelated; another, associated with jaundice, demonstrated subacute hepatitis, and 2 others had liver lesions similar to those described by Sabin and Aring.[5] In a case reported by Parker and Adams[6] cellular infiltration of the portal areas had occurred, but the hepatic cells were normal. Their description, together with the clinical picture, suggests infectious mononucleosis rather than hepatitis. In the case reported above, the necrosis and cellular infiltration within the liver lobules was marked; this finding is typical of acute hepatitis.[7] From these observations it appears that histologic changes in the liver are unusual in the Guillain–Barré syndrome and, when present, are a reflection of the associated disease.

The nature of the association between the Guillain–Barré syndrome and a variety of mild systemic diseases remains a mystery. Stillman and Ganong[8] believed that the neuropathy might be a hypersensitivity reaction related to antecedent infection in the same manner that rheumatic fever is related to bacterial infection.

Following this hypothesis they treated a patient with ACTH, and the results were excellent. In the case reported above, improvement was noted on the day after ACTH therapy was begun. Improvement in the neurologic disease continued even after ACTH had been stopped although there was a subsequent relapse in the hepatitis. The second course of ACTH seemed to have a good effect on the hepatitis, but had no influence on the rate of improvement of the neuropathy. Therefore, no definite conclusion concerning the value of ACTH in the Guillain–Barré syndrome may be drawn from this case.

Summary

A case of Guillain–Barré syndrome associated with acute hepatitis is described. Improvement, perhaps coincidental, accompanied the use of ACTH.

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MEDICAL PROGRESS

PEDIATRIC RADIOLOGY*

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DURING the past few years there have been tremendous advances in pediatric radiology. The number of articles devoted to this subject has increased so greatly that the task of the reviewer becomes difficult in selecting the articles of most value. In a review of moderate length one can hope to cover only a few of the important contributions recently made in the field of pediatric radiology.

Many of the diseases and abnormalities observed in children present radiologic findings similar to or identical with those seen in adults. Studies of these diseases among children reveal only the relative incidence and, at times, the severity of the impact on growth. Many other diseases, however, are unique to childhood, and it is with these that this review chiefly deals. An attempt is made to group the diseases discussed according to the structures chiefly involved. However, it is evident that this is not altogether satisfactory since in infants and children disease manifest in one organ system of the body may be equally manifest in another and disease anywhere in the body may affect the growth and development of the entire organism.

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Diseases of the Chest

It has been known for a long time that pulmonary hemosiderosis is frequently associated with long-standing passive congestion of the lungs. It has

been most frequently observed in rheumatic heart disease with involvement of the mitral valve. This condition may be seen in children without associated heart disease or chronic passive congestion. It may be associated with hypochromic pseudohemolytic or hemolytic anemia and has been seen with aplastic anemia in which transfusions have been followed by numerous reactions. Primary pulmonary hemosiderosis may occur in the absence of rheumatic heart disease, chronic passive congestion or anemia.[1] The etiology is obscure, but the roentgenographic picture may at times be characteristic. As a rule the deposits of hemosiderin are scattered diffusely throughout each lung, but they may be located predominantly in one lung or in a lobe. In the early stage the roentgenogram will show a fine, granular infiltration throughout the involved lungs. As the disease becomes more advanced and the deposits greater in number and extent, these fine, granular shadows become confluent so that the opacity of the lungs becomes considerably increased. A severely involved lung may appear wholly opaque on a normally exposed roentgenogram, but the overexposed or Bucky film of the chest usually reveals infiltrates by the finely granular pattern, or stippling of the lungs.

The occurrence of pulmonary hyaline membranes in newborn infants has puzzled pediatricians and pathologists for many years. The formation of the membranes is a controversial problem, and there may be several different ways in which the pathological picture may be produced.[2] It is not certain that it is caused only by aspiration of amniotic fluid. The possibility exists that pulmonary edema and excess fluid in the bronchi of intrinsic origin are also responsible. The condition occurs predominantly in premature infants, particularly those born by cesarean section or in association with other conditions that could produce intra-uterine anoxia or asphyxia. In spite of the frequency with which this condition is met at autopsy, no definite article on the x-ray appearance of the chest has as yet appeared. However, enough is known of the roentgenographic findings to indicate that in most cases x-ray examination of the chest might be helpful in establishing the presence or absence of this condition. In nearly all cases the lungs appear to be of adequate or of increased volume, but throughout each lung there is a fine lacework pattern of increased density, which presumably represents the numerous areas of resorption atelectasis with associated areas of unexpanded lung. A moderate amount of compensatory emphysema appears from the roentgenographic examination to be associated with this atelectasis. It is probable that this appearance is to be confused only with interstitial edema and with the poorly understood interstitial pneumonitis occurring in newborn infants.[3]

Diseases and Abnormality of the Skeleton

Examination of the long bones of apparently healthy infants in the neonatal period occasionally shows duplication of the cortical shadow or a "double-contour effect" that is frequently mistaken as evidence of systemic disease. An explanation for this shadow has for a long time been wanting, but it now appears from the work of Hancox et al.[4] that the "double-contour effect" is due to local exaggeration of normal appositional growth of bone and is a normal radiologic finding, particularly in underweight or premature infants.

Savignac[5] has reviewed reported cases of chondrodystrophia calcificans congenita, which is characterized by minute calcific deposits in the cartilage of primary or secondary ossification centers. The deposit may involve the tracheal and bronchial cartilage rings and may at times appear as a manifestation of an osteochondrodystrophy. The x-ray changes are too well known to require further description here. An abnormality that in many ways is similar, but usually localized to one knee and ankle, has been referred to as tarso-epiphyseal aclasis.[6] Here, too, the cartilage about the secondary ossification centers or the tarsal bones may show punctate calcific deposit, but in addition there is usually considerable overgrowth of cartilage and this proliferation may be so extensive as to produce a palpable mass. Eventually, the punctate calcific deposit becomes confluent and intimately associated with the underlying bone and may be replaced by apparently normal bone. The deformity caused by this lesion may be severe and disabling.

Gargoylism, also known as Hunter-Hurler disease, dysostosis multiplex or lipochondrodystrophy, ranks third in frequency among the generalized intrinsic dystrophies of the skeleton. It is exceeded in frequency only by achondroplasia and osteogenesis imperfecta.

Since the original description of this condition by Hunter in 1917 knowledge has grown slowly. Recently, Caffey,[7, 8] in a significant contribution, has had the opportunity to observe the initial changes of gargoylism in the skeleton of young infants and to observe its progression into the full-grown and unique abnormality of bone. It is of interest to review the development of this condition in one of the patients observed by him. Shortly after birth the child exhibited the coarse, ugly features, the broad nose and large nostrils that are frequently pathognomonic of gargoylism. The eyes were widely spaced, the face was wide below the orbits, and the cheeks were protuberant. The soft tissues covering the alveolar ridges of the upper jaw appeared to be thickened. The ears were large and low in position. The fingers were long and slender and suggested arachnodactyly. Roentgenographic examination of the skeleton on the eighth day of

life disclosed a generalized disease characterized by rarefaction and irregular subperiosteal cloaking of the shafts of the long bones. There was spurring and irregular mineralization of the epiphyseal plates. These changes suggested rickets, renal osseous dystrophy or hyperparathyroidism. However, none of these diagnoses could be confirmed by laboratory analysis, since the only abnormality was an increase in the alkaline phosphatase activity to 46 Bodansky units. The rickets-like changes disappeared by the tenth to the fifteenth week, and the subperiosteal new bone became thicker and denser. At the same time there appeared to be expansion of the shafts of the bone with diminution in the thickness of the cortical walls, and by the twenty-sixth week these changes were marked. By the fifteenth month dorsal angulation of the proximal humerus appeared whereas the distal end of the humerus seemed to be pinched off, as did the extremities of the now swollen and shortened metacarpals. Later the patient exhibited the classic signs of complete gargoylism. Caffey believes that it is possible that the skeletons of all gargoyles go through a similar initial osteoporotic phase, although it is probable that in many cases the osteoporotic phase is much milder and more slowly progressive and possibly could be identified on the x-ray films only with difficulty.

The explanation for these early bone changes is as yet unsettled. Certainly, many of the changes were probably instituted during fetal life and may well represent early and active infiltration of bone and infiltration beneath the periosteum of the complex lipid polysaccharides, whose accumulation, in the opinion of many workers, must place gargoylism among the thesaurismoses or storage diseases. Certainly, the disease is not infrequent and should be recognized not only by inspection of the patient, but also by roentgenographic examination of the skeleton. It should be suspected in infancy if the osteoporotic stage of gargoylism is identified and the appearance of the patient in any way suggests the possibility.

Recent studies of the age distribution in osteoid osteoma indicate that perhaps 40 per cent of reported lesions have been found in children fifteen years of age or younger.[9] Characteristically, in the long bones an osteoid osteoma may be identified by a radiolucent area a few millimeters in diameter that is surrounded and often obscured by an osteosclerotic area several centimeters in diameter. There may be extensive subperiosteal new-bone formation. However, the recognition of this lesion may become quite difficult when it involves the smaller bones, a secondary ossification center of a tubular bone or the spine. When the lesion involves a secondary ossification center or one of the processes of the vertebral column subperiosteal new bone is not to be expected, and in these sites the osteoma even more closely resembles a bone abscess than when seen in the long bones. A number of patients have been observed in whom the typical boring pain preceded by several months the identification of the lesion on x-ray examination.

Diastematomyelia[10] is being recognized with increasing frequency, and over 30 patients with this abnormality have been identified at the Children's Hospital. Diastematomyelia is an embryologic defect of the neural axis and spinal column with a sagittal division of a segment of the cord associated with other anomalies of the vertebras. There is a midline osseous spicule arising from the posterior aspect of a vertebral body. This osseous septum passes posteriorly and transfixes the spinal cord or cauda equina. The split cord passes on either side of the midline spicule, resulting in widening of the neural canal. On x-ray examination of the spine localized widening of the neural canal with increased width of the interpedicular spaces is seen, with a midline osseous spicule often recognizable as an irregular or linear fragment of bone lying in the midline over the neural canal. Only rarely can it be identified in the lateral projection, but in the lateral film diminution in the anteroposterior diameter of the vertebral body, partial failure of segmentation or hemivertebras of the bodies may be seen. The lesion has been identified in the dorsal and lumbar regions. No report of a transfixing bony spicule in the cervical region has yet appeared.

The importance of early surgical treatment of primary craniosynostosis is stressed by McLaurin and Matson.[11] They report results in 36 patients operated on in the first six months of life. Of these, 19 presented closure of the sagittal suture alone, 10 of coronal closure, and 7 of multiple suture or miscellaneous involvement. It is the purpose of surgery to provide artificial sutures that will remain patent during the period of most active brain growth. The brain normally doubles in weight during the first seven months. The best cosmetic results can be obtained by early operation, and possible mental retardation, visual impairment or severe increased intracranial pressure is thereby avoided. Roentgenographic examination of the skull is of extreme importance in demonstrating the deformity of the skull and of the distribution of synostosis. In all cases it should be possible to make the diagnosis during the first few weeks of life. The deformity of the skull produced by synostosis is usually characteristic, but it may be somewhat more difficult to identify the actual site of sutural closure. This is particularly true in synostosis of one coronal suture, which leads to asymmetry of the skull.

After the first two months of life, in addition to identification of a closed suture, it is usually possible to recognize the presence of increased intracranial pressure by separation of other sutures or, if all sutures are closed, by the great accentuation of digital markings present in the inner table of the

skull. Because the surgeons believe that the best results are obtained by operating very early in life and the radiologist can make an exact diagnosis at birth, it is incumbent on the clinician to suspect this lesion in the presence of any abnormality of contour of the calvarium and to have a careful roentgenographic examination of the skull carried out.

A congenital dermal sinus forms in the middorsal aspect of the embryo at the site of separation of the neuroectoderm from the epithelial ectoderm. Many of these congenital dermal sinuses are associated with cystic expansion at the inner end, which may represent either a dermoid or epidermoid.[12] The expanded portion of a congenital sinus, if located within the spinal canal or cranium, may interrupt neurologic function by local compression or may produce interruption of the circulation of cerebrospinal fluid. Meningitis or abscess formation may be present. It is essential that in the presence of any unexplained meningitis, especially if it is due to hemolytic *Staphlococcus aureus*, the skin surface along the midline posteriorly be examined for skin dimple, palpable mass or sinus opening. Although in all cases in which a sinus passes through the calvarium to enter the posterior fossa a defect can be found at operation, only on occasion is roentgenographic examination helpful. Frequently, the sinus opening is minute and runs obliquely through the table of the skull so that only by chance can it be satisfactorily seen on the roentgenogram. Occasionally, the opening may be of such size, up to 5 mm. or more, with sclerosis of the margins, that it can be easily seen on the film. Dermal sinuses over the back may not be associated with a spina bifida or defect in the lamina so that the presence of an intraspinal mass associated with a congenital dermal sinus cannot be excluded by roentgenographic examination alone. Occasionally, osteomyelitis, erosion of bone or widening of the interpedicular spaces suggests the presence of an intraspinal dermoid or epidermoid.

Infantile cortical hyperostosis is now known to be a common disease of infancy. In most cases the condition appears to be self-limited and subsides without residual deformity of the bones, but in a few, as in that reported by Caffey,[13] if there is extensive subperiosteal proliferation of the radius and ulna or of the tibia and fibula, the raised periosteum of one bone may come in contact with that of the other; this has on occasion resulted in the formation of bone bridges, or syncytia, and these bridges may interfere seriously with the function of the forearm. In addition, apparent expansion of the medullary cavity of a bone with marked widening has occasionally been noted, so that a new cortex is formed at what appears to be the limit of the raised periosteum. These changes may persist for a long time, but eventually the contour of the bone may be re-established in normal fashion.

There have been a number of articles devoted to the study of the roentgenographic aspects of bone growth and the alteration in the pattern of development produced by disease, chemical agents or irradiation. A number of conditions produce increase in density of the zones of provisional calcification at the ends of growing bones. Follis and Park[14] believe that it is important to distinguish between zones of increased density and transverse lines of increased density since the pathogenesis of the two may be entirely different. Zones of increased density result from an overproduction, and usually associated failure of destruction, of calcified cartilage matrix material whether caused by nonspecific or specific mechanisms. This matrix may be covered with varying amounts of bone. Transverse lines of increased density result from bone formation in a horizontal plane on the undersurface of the cartilage.

Careful study of the influence of irradiation on the growth and development of the spine has shown that the deleterious effect is proportional to the amount given and inversely proportional to the age.[15] One thousand r or less delivered to the spine at any age usually causes no detectable abnormality in the appearance or growth of the vertebras. A larger amount of irradiation, particularly if given to the infant or young child, may produce lines of increased density, irregularity in serration of the vertebral margins or gross deformity of contour and interference with development, resulting in a vertebral body resembling in many ways the deformed body in osteochondrodystrophy. Exostoses of the flat or long bones may be initiated by similar amounts of irradiation. It seems from this study that scoliosis will not result if radiation is given uniformly over a segment of the spine so that unilateral diminution in the rate of growth is avoided. Although the changes observed appear to be significant they do not appear to be sufficiently severe to contraindicate the judicious and careful administration of irradiation in the treatment of cancer in infancy or childhood.

Russell and Russell[16] review the problem of damage to the fetus caused by x-rays in the pregnant patient. It appears from their study that there is a critical period for the production of a majority of gross abnormalities resulting from radiation in mice. In man this would correspond to the second to sixth week of gestation. Irradiation administered in more advanced stages after the sixth week in man will probably induce less obvious and possibly more delayed effects.

Radiation may also have a deleterious effect on the soft tissues lying in the field of radiation, and there may be diminution in the rate of growth or delay in development of a part distal to the field of radiation.

Lesions of the Esophagus and Gastrointestinal Tract

The frequent association of tracheoesophageal fistula with atresia of the esophagus has long been known. Congenital tracheoesophageal fistula not associated with atresia of the esophagus occurs less frequently. Ferguson[17] reports 5 cases of this unusual congenital defect seen at one clinic. He discusses the theories of the development and believes that the most plausible is that there is an arrest in the development of the lateral cell masses that separate the primitive foregut tube into the esophagus dorsally and the trachea ventrally and that a congenital fistula is probably well established by the seventh to eighth week of fetal life. The diagnosis is difficult, and the symptomatology variable. The presence of a fistula should be suspected in an infant who has frequent attacks of aspiration pneumonitis with choking and possibly cyanosis during feedings. In most cases a positive diagnosis can be made only by proper roentgenographic examination. Satisfactory visualization of a tracheoesophageal fistula can usually be obtained if the patient is examined in the lateral decubitus position while swallowing iodized oil or thin barium mixture. The fistulas vary in length and in diameter and usually occur within a few centimeters of the bifurcation of the trachea.

The fistula runs backward and downward from the trachea to the esophagus. Some may be so small that only a minute thread of the opaque medium can be seen, but flooding of the trachea can usually be recognized. It is to be remembered that most infants are unable to swallow iodized oil satisfactorily and that a considerable amount of material will be aspirated into the trachea. This may confuse the picture and make diagnosis difficult. Occasionally, the fistula can be delineated after the instillation of iodized oil into the trachea. The lesion is important because despite the fact that it is amenable to surgical correction the disease remains undiagnosed in many patients, who subsequently die of pneumonia.

From a number of recent papers it has become clear that abnormalities of the lower esophagus are not an uncommon cause of vomiting in infancy.[18-23] The exact nature of some of these abnormalities is not clear, but all have in common the incompetence of the gastroesophageal-valve mechanism, permitting reflux of gastric content into the esophagus. This results in regurgitation and vomiting, peptic esophagitis, ulceration and hematemesis. A number of patients appear to exhibit only incompetence of the valve mechanism. In others there appears to be extension of the gastric mucosa into the lower few centimeters of the esophagus, but more commonly there is a minor degree of partial extension of the stomach into the thorax. Paraesophageal and true esophageal hiatus hernias also occur. During roentgenoscopic examination of a patient with one of these abnormalities gastroesophageal reflux is nearly always observed. If a portion of the stomach extends above the diaphragm the esophagus has a normal course without redundancy, but ends above the diaphragm at the highest point of a small or thoracic loculus of stomach. In many cases a constriction representing the cardia can be identified, and below this there is often slight asymmetrical expansion in which gastric rugae can be identified. Usually, an abrupt transition between the coarse vertical rugae, representing gastric mucosa, and the fine linear rugal markings of the esophagus can be identified. In many patients esophagitis and peptic ulceration occur in the esophageal mucosa just proximal to the junction with the gastric mucosa. This can be identified by irregularity of contour, spasm, stenosis, pseudodiverticulum formation and actual visible ulcer.

Ulceration of the lower esophagus is probably the most frequent ulceration of infancy, but ulcers of the stomach and duodenum are being reported with increasing frequency in both infancy and childhood.[24] Acute ulceration of the stomach or duodenum in infancy is rarely found as an isolated phenomenon, but is more commonly associated with circulatory disturbances of the gastrointestinal tract, sepsis, cerebral anoxia and lesions of the brain. Lemak[25] reports that of 18 infants with ulceration 50 per cent gave evidence of brain damage and 66 per cent were premature.

The incidence of chronic ulceration of the stomach or first portion of the duodenum is controversial. Certain and possibly somewhat overenthusiastic authors have reported a very high incidence of duodenal ulcer in childhood.[26] It is probably not possible to arrive at a satisfactory figure of the incidence, but the condition is certainly more common than is generally suspected.

Knowledge of Hirschsprung's disease[27, 28] and of the aganglionic colon is accumulating rapidly, and it is now known that physiologic obstruction of the large bowel due to complete absence of ganglion cells throughout the colon or in a segment of the colon is one of the important lesions of infancy and childhood. Originally, it was thought that most patients with Hirschsprung's disease had a segment of the distal colon that was without ganglion cells, but it is now apparent that the entire colon, or a very long segment, may be affected.

Many of these patients probably do not survive sufficiently long for the megacolon to develop, so that x-ray diagnosis may be difficult. Occasionally, if the entire large bowel is without ganglion cells, the colon is short and appears markedly underdeveloped. It can be readily filled with barium by enema, but evacuation of the barium does not occur satisfactorily. However, distention of the

small bowel and normal colon proximal to a long segment of colon without ganglion cells is usually evident during the first few weeks of life. A number of patients have been seen where there appears to be defective innervation of both the small and large bowel. This condition does not appear to be compatible with survival for any reasonable period.

The roentgenographic manifestations of other forms of obstruction of the small and large bowel have recently been clarified.[29, 30] Obstruction due to impaction of inspissated meconium in the distal small bowel may mimic the x-ray picture produced by meconium ileus, where there is altered viscosity of the meconium from pancreatic achylia. In meconium ileus it is usually possible to make a diagnosis by examination of survey films of the abdomen. Multiple dilated loops of proximal bowel are seen. The meconium masses within the distal small bowel always lie proximal to the ileocecal valve and can usually be identified by the small bubbles of gas that have been forced into this altered meconium.

With simple meconium plugging and inspissation the large masses of meconium are usually not present, but small accumulations may be identified in the distal bowel. Fine calcific deposits may occur in the altered or inspissated meconium. Calcific deposit may also occur either in the lumen or in the wall of bowel proximal to a point of congenital atresia. Perforation of the bowel with any of these lesions is not uncommon, and calcified material may be extruded into the peritoneal cavity. If this type of calcific deposit is defined on the film a diagnosis of meconium peritonitis is not warranted unless there is other evidence of perforation. In meconium peritonitis the calcific deposit that formed in the peritoneal cavity about extruded epithelial cells can usually be defined as outlining the peritoneal surface of the abdominal cavity or its contained organs.

Congenital Heart Disease

With the current increasing emphasis on the diagnosis and treatment of congenital heart disease the role of the x-ray examination has become more clearly defined. In the detection of congenital malformations, particularly in early infancy, the x-ray and fluoroscopic technic has severe inherent limitations. In the differential diagnosis, and in the evaluation of the status of the patient on which to base a therapeutic approach, x-ray studies become a highly significant factor when integrated with clinical and laboratory data. This subject was recently reviewed in this journal.[31] It has become increasingly apparent that the physiologic and anatomic variations resulting from persistent patency of the ductus arteriosus are exceedingly wide. An increasing number of patients with a patent ductus have been found without the traditional to-and-fro murmur, presenting either no murmur or one limited to systole. These patients apparently have in common a certain degree of equalization of the pulmonary and systemic pressures. As a result the radiologic picture is one of varying degrees of enlargement of the right ventricle superimposed on the "typical" configuration of enlargement of the left ventricle and atrium and prominent pulmonary artery and vasculature. Thus, with this balanced load the heart gradually assumes the configuration similar to if not indistinguishable from the Eisenmenger complex.

An increasing number of patients with clinically significant patency of the ductus are being observed who show either complete absence of murmur or atypical murmurs. In our experience these patients have all shown the "Eisenmenger physiology" on x-ray examination and represent either excessively large ducti or moderate-sized shunts of fairly long standing. In the excessively large ductus the complex neurocirculatory reflex system apparently must raise the pulmonary pressure to a relative degree of hypertension or the infant would bleed into a state of systemic shock into his pulmonary capillary bed through the large hole in the side of the aorta. In the relatively smaller shunts of long standing, pulmonary hypertension is associated with definite peripheral arterial changes recognizable by the pathologist that appear to result in a peripheral pulmonary arterial resistance. Thus it becomes obvious that with these so-called "atypical" features the patent ductus ceases to have distinctive diagnostic features readily recognizable by everyday diagnostic technics. It is here that retrograde aortography has become a definitive procedure. In fact, this procedure is probably indicated in any acyanotic patient with nondescript murmurs, pulmonary vascular engorgement and a more or less balanced enlargement of the right and left ventricles in whom the clinical diagnosis cannot be easily established if the diastolic blood pressure is low. The retrograde aortogram is also the only procedure that may at times differentiate the pulmonary aortic fenestration and high defect of the ventricular septum from the patent ductus arteriosus.

Of the complex congenital malformations of the heart producing cyanosis the presence of deficient pulmonary blood flow is the most amenable to surgical treatment. Short of detailed catheter studies, simple roentgenographic examination of the lung fields probably yields the most reliable evidence of the presence or absence of deficient pulmonary blood flow. In the relatively common tetralogy of Fallot the roentgenographic evidence of diminished pulmonary vasculature and lowered tolerance of activity becomes the crucial factor in the selection of patients for operation.

Conclusions

No field of diagnosis is expanding more rapidly than pediatric roentgenology. Satisfactory roentgenologic criteria for the diagnosis of well known conditions are being established, new x-ray signs are being disclosed, and many diseases formerly thought to be rare are being recognized with increasing frequency.

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MEDICAL INTELLIGENCE

EVALUATION OF TUBELESS GASTRIC ANALYSIS*

Report of 90 Determinations by Intubation and Tubeless Methods Made Simultaneously

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GLENS FALLS, NEW YORK

IN 1950 Segal and his associates[1] introduced a method for determining free gastric hydrochloric acid based on release of quininium cation from a synthetic ion-exchange resin by the hydrogen ion in gastric secretion. The resin granules were given orally, in a dosage of 2 gm. Two-hourly urine samples were then analyzed for quinine, the presence of quinine in appreciable concentration indicating free gastric hydrochloric acid. Later, Segal et al.[2] described the procedure in greater detail, reporting results in 106 patients. The test was found to have a high degree of accuracy when compared with gastric analyses conducted previously on samples of gastric secretion removed by the usual intubation technic.

The purpose of the present study is to evaluate the tubeless method by means of simultaneous determinations using both technics.

Materials and Methods

Ninety duplicate tests were run on 88 patients. Histamine (0.275 mg. of histamine diphosphate) injected subcutaneously was the stimulant in all but 1 case (Case 35), in which 50 cc. of 7 per cent ethyl alcohol was used. In all these patients one or more of the usual indications for gastric analysis were present. Most of the patients were on the medical service.

The technic described by Segal et al.[2] was modified to allow simultaneous determinations by both methods. The patient is fasting on the morning of

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the test. The morning urine sample is saved to be used as the control blank. A gastric tube is passed in the usual manner, and the fasting gastric contents are removed for analysis. Histamine diphosphate (0.275 mg.) is injected subcutaneously, and the time noted. Half an hour later gastric contents are withdrawn for analysis, and the tube is removed. The patient is instructed to void; this sample is discarded. Two grams of synthetic quinine-bearing resin (Diagnex*) is then given with half a glassful of water, and one makes sure that all the granules are swallowed; a small additional quantity of water is usually necessary. Exactly an hour after taking the resin the patient voids completely. All of this specimen (Sample 1) is saved. Exactly two hours from the time the resin was taken the patient again voids completely (Sample 2). The fasting sample and samples 1 and 2 are sent to the laboratory for analysis for quinine. The patient is not permitted to eat, drink or smoke during the test, and is kept lying quietly in bed.

Examination of Gastric Contents

Both the fasting and half-hour samples of gastric contents are examined as follows: volume is measured; abnormal features, such as the presence of bile or blood, are noted; 4 drops of Töpfer's reagent (0.5 per cent para-dimethylazobenzene) is added to 10 cc. of gastric sample, a red color indicating free acid. The sample is then titrated with one-tenth normal sodium hydroxide to a salmon-pink neutral point. The volume (in cubic centimeters) of sodium hydroxide used multiplied by 10 gives degrees of free hydrochloric acid.

Examination of Urine Samples

The fasting sample and samples 1 and 2 are examined for quinine according to the method of Segal et al.[2,3] This method involves ether extraction of the alkalinized urine followed by extraction of quinine from the ether by one-tenth normal sulfuric acid.[4] The sulfuric acid solution is then viewed in ultraviolet light and compared with standard quinine solutions, a total concentration of more than a trace (0.012 mg.) of quinine indicating free gastric hydrochloric acid according to the criteria of Segal and his co-workers.[2]

Results

Seventy-six cases showed free acid by both methods (Table 1). Of these, 74 showed a total urinary concentration of greater than + (0.040 mg.). In 1 case the urinary excretion of quinine was less than +, but was greater than 0.012 mg.

One case (Case 77) revealed 32 degrees of free acid in the half-hour gastric specimen, and a total quinine excretion of less than 0.012 mg. This case was the only discrepant result in this study.

Eleven cases (Cases 78 to 88) demonstrated achlorhydria by both methods. In 2 of these the determinations were repeated. In the cases showing achlorhydria the clinical diagnoses were primary achlorhydria (8 cases) and pernicious anemia (3 cases).

Table 1. *Gastric Analysis by Simultaneous Methods.*

Case No.	Degrees of Free HCl		Urine Quinine Concentration	
	Fasting	Half-hour	1 hr.	2 hr.
1-76	0-44	4-116	Faint trace to ++	Faint trace to ++++
77	Trace	32	Faint trace	Faint trace
78-87	0	0	0	0
88	0	0	0	Faint trace

Discussion

The tubeless method is highly accurate as compared with analysis of gastric samples removed by intubation. There is no apparent quantitative correlation between the two methods, high excretion of quinine frequently being associated with low acid values, and vice versa.

No discomfort was caused any of the patients in this series that could be attributed to the tubeless method.

Summary and Conclusion

A series of 90 determinations of free gastric hydrochloric acid were made on 88 patients by simultaneous intubation and tubeless methods. The results indicated excellent agreement between the two methods. The tubeless method is recommended for the routine qualitative determination of free gastric hydrochloric acid.

We are indebted to Mr. John Dever for technical assistance.

*Kindly supplied by E. R. Squibb and Sons, New York City.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39281

PRESENTATION OF CASE

A forty-year-old single woman was admitted to the hospital because of swelling of the ankles.

Although the patient had felt more tired than usual, had lost her appetite and had lost 10 pounds (going from 110 to 100 pounds) during the few months before admission, she considered herself well until ten days before entry, when she noted the onset of severe shortness of breath on climbing stairs. There were no other symptoms such as cough, fever or edema at this time. Three days before entry she noted swelling of the ankles for the first time.

The patient had had seizures that were well controlled by Dilantin and phenobarbital, which she had taken for the two years before admission. The past history was otherwise noncontributory.

Physical examination showed a thin and poorly nourished woman who was in no acute distress but appeared chronically ill. There were increased breath sounds in both apexes; the lungs were otherwise clear. The heart was normal. The abdomen was rotund and appeared distended. It was firm and doughy, with a sensation of resistance, and minimally tender throughout. There was dullness in the flanks, but no fluid wave. No masses or organs were felt. Pelvic examination was negative. There was +++ edema of the legs and ankles.

The temperature was 101°F., the pulse 100, and the respirations 20. The blood pressure was 120 systolic, 85 diastolic.

Of two urine specimens, one had a specific gravity of 1.018 and was otherwise normal; the other gave a ++ test for albumin, and its sediment contained occasional red cells and was loaded with white cells. A urine culture was negative. Examination of the blood revealed a hemoglobin of 11.4 gm. per 100 cc. and a white-cell count of 13,000, with 70 per cent neutrophils, 28 per cent lymphocytes, and 2 per cent monocytes. On smear the red cells exhibited ++ variation with a tendency to macrocytosis. The serum nonprotein nitrogen was 12 mg., the total protein 5.0 gm., the albumin 3.0 gm., and the globulin 2.0 gm. per 100 cc. The cephalin flocculation was ++ in forty-eight hours. A stool specimen was guaiac negative.

A roentgenogram demonstrated bilateral pleural effusions, greater on the left, where the fluid was at the level of the fourth rib in the axillary line (Fig. 1). There were scattered nodular densities above the fluid, somewhat greater in number at the level of the right second anterior interspace. There was also a suggestion of some vague granular densities in the aerated portion of the left lung. There were irregular linear streakings in the right lung above the fluid. The heart was of normal size. Films of the abdomen showed a generalized increase in density throughout the abdomen, with bulging in each flank suggestive of free fluid within the peritoneal cavity. There was a vague suggestion of an abnormal mass above the distal portion of the transverse colon. The spleen was somewhat enlarged. The renal shadows were not well defined. An intravenous pyelogram was normal. A barium-enema examination was negative except for diverticula in the sigmoid colon. A barium-meal examination disclosed distinct fixation of the stomach and duodenal loop, without definite evidence of intrinsic disease (Fig. 2). The third portion of the duodenum appeared to be displaced slightly in an upward and

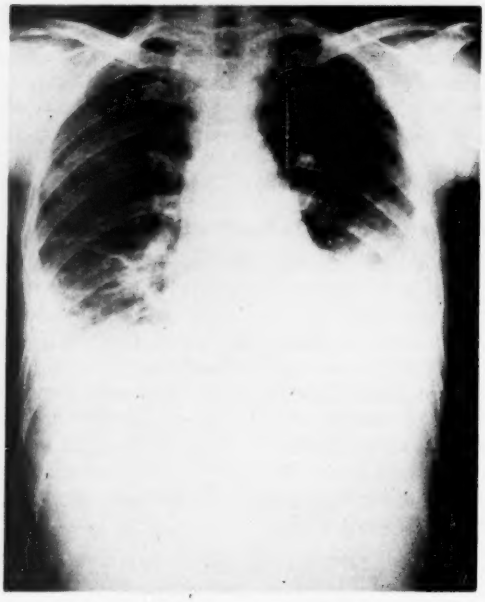

FIGURE 1. *Roentgenogram of Chest.*

lateral direction. There was slow progress of the barium through the bowel. Scattered areas of small bowel were dilated. Most of the bowel loops appeared clustered in the midabdomen, and were probably fixed in position. The terminal ileum appeared ragged in outline.

A thoracentesis on the left was performed, and 650 cc. of clear, straw-colored fluid, having a specific gravity of 1.014, was removed. It contained

FIGURE 2. *Barium-Meal Examination.*
Barium is dispersed in the small-bowel loops (which the fluoroscopist found to be fixed). Arrows point to the irregular margin of the terminal ileum.

1603 red cells and 1 neutrophil per cubic millimeter. Pathological examination of fluid revealed no tumor cells. Routine culture demonstrated no growth. Injection of 1:100,000 of old tuberculin caused a 3-mm., indurated erythematous reaction in forty-eight hours. On the fourteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. F. DENNETTE ADAMS*: I should like to ask a few questions. What can you tell me about the patient's menstrual periods?

DR. BENJAMIN CASTLEMAN: Catamenia had started at the age of twelve, and the periods were regular and lasted for six days. The last period had occurred seven months before entry; the last two periods had been regular but had lasted for only one or two days.

DR. ADAMS: I can assume that the rectal examination was negative?

DR. DANIEL S. ELLIS: Yes.

DR. ADAMS: The urine specimen, showing albumin, leukocytes and red cells, was not collected by catheter; the negative specimen was collected by catheter?

DR. ELLIS: That is correct.

DR. ADAMS: Then I can exclude infection of the urinary tract. Does the statement regarding seizures mean that they existed for two years or only that the anticonvulsant drug had been given for two years?

DR. ELLIS: The epilepsy was discovered two years before admission. At that time the patient had a severe exacerbation of the epilepsy and was almost psychotic owing to severe status epilepticus. She did improve.

DR. ADAMS: Unless they are due to an expanding lesion or trauma, convulsive seizures starting as late as thirty-eight are unusual. So one must wonder if this patient's spells were related to the disease that had recently developed. The improvement steers one away from connecting the two unless it could be attributed to the drug therapy. If the seizures had progressed, one would indeed be inclined to relate the seizures and later indications of trouble to the same cause.

I always prefer to speculate about the diagnosis before seeing the x-ray films, but in this case, especially since there is a discrepancy between physical and x-ray findings, I ask Dr. Wyman to discuss them now.

DR. STANLEY M. WYMAN: The chest films demonstrate a fairly large pleural effusion on each side, the larger amount of fluid being on the left. There are small hazy densities in both lung fields, the largest number being in the right second interspace. The heart shadow, as nearly as I can outline it, seems to be normal (Fig. 1).

DR. ADAMS: Is that a healed primary lesion of tuberculosis—the so-called Ghon tubercle?

DR. WYMAN: It could be a small calcified lung focus. There are no definite calcified lymph nodes at the hilus, but that does not exclude the possibility by any means. The linear densities in the lower lung fields are the result of atelectasis.

DR. ADAMS: Can I assume that fluoroscopically the heart was also normal? Were the pulsations abnormally small?

DR. WYMAN: I do not know the answer to that.

DR. ELLIS: There was no suggestion clinically that she had cardiac enlargement.

DR. ROBERT S. PALMER: Is there not a slight bulge in the left border of the heart that is not quite normal?

*Physician, Massachusetts General Hospital.

DR. WYMAN: I think I should pass that as being within the range of normal. The abdomen has an over-all hazy, ground-glass appearance. There is some bulging of the flanks. The psoas muscle, kidney and other visceral outlines are poorly seen, which suggests fluid. The spleen may be slightly enlarged. There is a lesion in the right femur that was not commented on; I do not believe we have any information on that so that perhaps I should not have mentioned it. On the film from the pyelogram the collecting passages in both kidneys, and as nearly as I can outline them, the ureters appear normal. The barium-enema examination shows a normal colon without localized defects. The fluoroscopist noted definite fixation of the bowel. He could not move the stomach or the loops of small bowel in the normal fashion; this was a positive observation. Some loops of lower jejunum or upper ileum seem somewhat ragged on this film, but this may be the appearance of the moment only. There is a tendency to flocculation of barium, but otherwise there is no definite localized abnormality (Fig. 2).

DR. ADAMS: Is it fair to inquire what sort of process flocculation suggests? I am not familiar with its implications. Does it mean that peristalsis is perhaps irregular and that the barium pools from time to time?

DR. WYMAN: It is believed to be the result of barium mixing with the contents of the small bowel. It is seen in deficiency states primarily — sprue or any debilitating disease. It is a nonspecific finding.

DR. ADAMS: In brief, we are faced with a patient who presented the following picture: fatigue and some loss of weight within a few months; recent and sudden development of dyspnea and ankle edema; fever; x-ray evidence of bilateral pleural effusion, and some parenchymal pulmonary process; clinical and x-ray evidence of intraperitoneal fluid and an abnormal gastric and intestinal pattern; and a somewhat enlarged spleen on x-ray examination.

A common cause of fluid in both pleural cavities and in the abdomen is some mechanical disturbance, but this can be excluded here. Certainly, there was nothing to suggest constrictive pericarditis — no pulmonary edema, no distention of veins, no restricted pulsation of heart, no pericardial calcium deposits and no enlargement of the liver. Nor do history and other findings provide anything to suggest thrombosis of the vena cava.

To have so many parts affected, the patient must have been suffering from a generalized systemic disease. There are two possibilities, tumor and infection. If it was tumor, what sort could it have been? The Meigs syndrome — fluid in one or both pleural cavities or the abdominal cavity, or both, associated with a fibroma of the ovary — must be mentioned. This can be promptly ruled out because of other factors, especially the fever and evidence of parenchymal pulmonary disease. Carcinoma of the cervix, when small, can be overlooked even in the presence of a remote metastatic lesion. But one that would give such widespread disease, especially in the abdomen, would certainly be manifested by bleeding or, on pelvic examination, by a mass, thickening or other sign of trouble. The same statement cannot be made for carcinoma of the ovary. Such a tumor is often so small as to be nonpalpable even under favorable circumstances of examination; in this case palpation was rendered more difficult by the status of the abdomen itself. Ovarian carcinoma often causes fever and often disseminates throughout the body. Another possibility is some intra-abdominal rather than intrapelvic malignant tumor. The most likely, and one that always deserves thought in an obscure case, is carcinoma of the pancreas. This frequently spreads by blood dissemination. It could well have been responsible, by such spread, for the fluid in the cavities and, by direct extension, for the stomach, intestinal and mesenteric changes. Tumor of stomach or bowel is unlikely. Nothing is recorded to suggest it: no anorexia, cramps, change of bowel habits or loss of weight. It would be most tempting to make a diagnosis of cancer of the pancreas; we could then explain the peripheral edema on the basis of phlebothrombosis, which, as we all know, is a common and often early complication of this disease. But with widespread disseminated carcinomatosis originating in the pancreas or other organ the patient should have been much sicker. Furthermore, if the observation that the spleen was somewhat enlarged is correct, this tends to lead one away from a diagnosis of cancer. Also as I look with my unpracticed eye at the films of the chest, the shadows do not conform to my idea of diffuse parenchymal carcinomatosis of the lungs. Is that a fair statement?

DR. WYMAN: That is always a moot question. The shadows are not typical of malignant lesions.

DR. ELLIS: The films were interpreted as being more suggestive of cancer than of anything else, were they not?

DR. WYMAN: I had not recalled that, and they do not impress me that way.

DR. ADAMS: Because of the absence of severe deterioration, the character of the lung x-ray films and the possibility of some splenic enlargement, I believe carcinomatosis should be excluded.

One can plead a better case for lymphoma, which could readily account for the fever, the abdominal signs, the pleural fluid, the pulmonary infiltration and the possibly enlarged spleen. But with lymphoma of this extent, enlargement of lymph nodes either peripherally or in the thorax, or greater enlargement of the spleen, should have been evident.

Finally, we come to infection. Here my remarks will be limited to tuberculosis. In support of tuberculosis are, in particular, the fever, the relatively sudden change in the state of the patient's health,

the pleural fluid and the changes in the lungs noted in the x-ray films. Is there any argument about the last statement, Dr. Wyman?

Dr. Wyman: No. I might go back to Dr. Ellis's remark and say that we have seen a great many cases in which tuberculosis and tumors were indistinguishable on films of the chest. Although I might favor tuberculosis over tumor in this case, I think the other point of view is perfectly reasonable.

Dr. Adams: In addition there is an old lesion that could be a Ghon tubercle, indicating previous primary tuberculous infection. The fluid present in the abdomen is not abundant nor is it "free" as one would expect in malignant peritoneal seeding or in portal obstruction as in cirrhosis of the liver. The intestines are matted together, the fluid must be pooled here and there, and intestinal function is hampered by some process. Although lymphoma could do this, it would be more likely in tuberculous peritonitis. Furthermore, we have a positive tuberculin test in high dilution. So it seems to me that, although lymphoma cannot be excluded, so-called subacute miliary tuberculosis is the diagnosis of choice. We think of this as an acute fulminating disease. But there is a form in which the spread occurs at a somewhat slower pace. Unless something is being withheld from me, my belief is that the operation was purely exploratory, or perhaps a peritoneoscopy. My second choice would be a diffuse malignant lesion, either lymphoma or carcinoma of the ovary.

Dr. Palmer: What did Dr. Adams* write about the firm and boggy abdomen in his book?

Dr. Adams: The word was "doughy" not "boggy." But in the discussion of tuberculous peritonitis, I described distention due to fluid, gas or both, scattered tumorlike masses formed by loops of intestine and parts of omentum matted together, or by encapsulation of fluid, and slight generalized spasm and tenderness. I interpreted the description in the case under discussion to mean something less than spasm but more resistance than would be found in the normal person. Perhaps in the forthcoming edition it would be well to use these terms.

A Physician: Can you tie in the epilepsy?

Dr. Adams: I do not see how this is possible. As implied earlier in this discussion, so-called idiopathic epilepsy beginning in midlife is unusual. One can speculate that seizures connected with the systemic disease provide a point in favor of tuberculosis, as opposed to carcinomatosis. A tuberculoma in the head might well remain stationary or perhaps regress; a malignant lesion would grow larger and, with time, probably cause more focal signs.

Dr. Alfred Kranes: Are you not leaning heavily on a questionable finding, the enlargement of the spleen?

Dr. Adams: The enlargement of the spleen is a questionable finding. I am really leaning more, but perhaps unwisely, on the x-ray films of the lungs and the history of the sudden change in the patient's status.

Dr. Briant L. Decker: What is your opinion about the lesion in the right femur that Dr. Wyman saw?

Dr. Adams: Dr. Wyman assured me that I could disregard that.

Dr. Wyman: That was probably an osteochondroma.

Dr. Ellis: There were several striking findings in this patient. First of all, she came to my office late one afternoon, having been sent to me from work because she had massive edema of the legs. That was the only thing she admitted was bothering her. I sent her to the hospital. When she was put to bed the edema apparently disappeared, though she had had edema up to the thighs. The palpation of the abdomen was difficult to describe, but I had no doubt that there was something abnormal within the abdomen. She did not have shifting dullness or a fluid wave, but I was certain that she had fluid.

Dr. Adams: That supports my opinion that this was loculated fluid.

Dr. Ellis: Correct. The third striking feature of the picture was the behavior. I did not know of the previous episode two years before admission, but at the time that she had come in for epileptic seizures she had been found to be paranoid and as a matter of fact was on the psychiatric ward for several days. Soon after she was admitted to the hospital this time she was very paranoid, and up until two days postoperatively I was constantly accused of keeping her in jail and doing things to make her miserable. She was unco-operative with every procedure and with everybody who was taking care of her.

On the basis of the negative pelvic examination, which Dr. Howard Ulfelder confirmed, the high fever and the obvious plastic process in the abdomen noted on x-ray examination and palpation, I believed that she had tuberculous peritonitis. We were unable to get any sputum; the gastric concentration was negative for tubercle bacilli; the guinea-pig inoculation was negative, and we had not received the report of the chest fluid or peritoneal fluid so we elected to do a laparotomy. We did not think that peritoneoscopy was to be considered in this patient, who we thought had a plastic peritonitis and loculated fluid, because of the danger of perforating the bowel. This was borne out at laparotomy, when the peritoneum was penetrated and the surface of the bowel was almost entered because we thought we were still in the space above the peritoneum.

Clinical Diagnosis

Tuberculous peritonitis.

*Adams, F. D. *Cabot and Adams: Physical diagnosis.* Thirteenth edition. 888 pp. Baltimore: Williams and Wilkins, 1942. P. 554.

Dr. F. Dennette Adams' Diagnoses

Subacute miliary tuberculosis.

Tuberculous peritonitis.

Tuberculous pleuritis, bilateral.

Anatomical Diagnoses

Tuberculous peritonitis.

Miliary tuberculosis.

Pathological Discussion

Dr. Ellis: Dr. Adams' predictions were correct: the patient had a plastic peritonitis in which the omentum and the peritoneum were densely matted together in locules. The whole omentum was a mass of nodules of yellow caseous material. The abdominal surface of the peritoneum was studded with yellow and white masses of nodules of various sizes. The intestine itself was matted together and when separated from the omentum or from the peritoneum looked like pieces of bread that had been buttered and pulled apart. It was a most unusual picture as far as the extent and severity were concerned; Dr. Donald S. King, Dr. Ulfelder and I had never seen anything this extensive. We wondered at the time whether we were dealing with some queer kind of sarcoma, histoplasmosis, toxoplasmosis or disseminated tuberculosis such as Dr. Adams diagnosed. Dr. Ulfelder took a biopsy of the omentum and of the peritoneum.

Dr. Castleman: Since the necrosis was so severe — not only yellow but also white in places — and since there was ascites Dr. Ulfelder thought he might be dealing with fat necrosis due to pancreatitis. Frozen section disclosed granulomas, characteristic of the caseous, necrotic type of fulminating tuberculosis.

Dr. Ellis: The patient was placed on 1 gm. of streptomycin intramuscularly and 50 mg. of isoniazid three times a day orally. The course postoperatively was striking. On the second postoperative day, all the paranoid ideas disappeared, and she became a very pleasant, co-operative person. Whether she had a tuberculoma in the brain or not I am not sure, but perhaps the result of the therapy is indicative that there was some process in the brain that the drugs had helped.

Dr. Castleman: The temperature went down too.

CASE 39282

Presentation of Case

A fifty-two-year-old housewife was admitted to the hospital because of weakness and giddiness.

For the previous three months her temperature had been elevated in the afternoon (to 100 to 102°F.), with afternoon and night sweats. At about the same time as the fever became manifest, she began to suffer from indigestion, with bloating and postprandial discomfort, but without real pain. She also became constipated. She was admitted to another hospital, where a gastrointestinal series, barium-enema examination, intravenous pyelogram, chest film, metastatic bone series and an electrocardiogram were reported as negative. One month before admission severe abdominal pain developed, which extended into the groins and back and was associated with distention, tenderness and constipation. She was admitted to a second hospital, where the pain subsided, leaving her slightly distended and constipated. Examination of the blood revealed a red-cell count of 2,500,000, with a hemoglobin of only 45 per cent, and two transfusions were given. Cystoscopy was negative. She was discharged and was at home a few days before the onset of weakness and giddiness caused her to come to this hospital.

For four or five years she was known to have been hypertensive. Three years before admission here she spent "one year" in bed, because of a "fatigued heart." She had taken digitalis since that time until two years before admission, when she underwent a cholecystectomy. Five months before admission she suffered from dysuria, with frequency, burning and pruritus vulvae. This attack subsided on treatment with sulfonamides. Other operations were an appendectomy, thirteen years, herniorrhaphy, six years, dilatation and curettage, five years, and excision of two cysts of the breast three years before admission. She had lived with her daughter, who had pulmonary tuberculosis, until two months before admission. In the five months before admission her weight fell from 130 to 118 pounds.

On physical examination the patient had a sallow complexion but was in no acute distress. There was no lymphadenopathy. The lungs were clear. The heart was not enlarged; there was a Grade 2 apical systolic murmur. The abdomen was rotund,

tympanitic, doughy and slightly tender in the right upper quadrant. Peristalsis was normal. There were no masses or palpably enlarged organs. There was an area of tenderness without redness or induration measuring 3 cm. on the medial aspect of the left thigh.

The temperature was 101.6°F., the pulse 126, and the respirations 18. The blood pressure was 140 systolic, 70 diastolic.

Examination of the urine was negative. Examination of the blood revealed a hemoglobin of 4.8 gm. and a white-cell count of 20,000, with 88 per cent mature and 4 per cent young neutrophils and 8 per cent lymphocytes. The red cells exhibited marked polychromasia and anisocytosis. There were 11.6 per cent reticulocytes. The platelets were increased in number. The hematocrit was 16 per cent. The serum total protein was 6.6 gm., the albumin 4.2 gm., the globulin 2.4 gm., the nonprotein nitrogen 26 mg., and the amylase 54 units falling to 33 units per 100 cc. after three days; the prothrombin time was 16 seconds (normal, 14 seconds). A Coombs test was negative, as was a blood culture. A stool guaiac test was ++++.

FIGURE 1. *Oblique Film from the Gastrointestinal Series. Arrow points to the ulceration, which lies either within the stomach or at the base of the duodenum, and extends into the mass.*

A roentgenogram of the chest was normal. On gastrointestinal series, the esophagus was normal. Extending from the posterior wall of the stomach in the prepyloric region was an irregular ulceration measuring 1.5 cm. associated with a soft-tissue mass 7 cm. in diameter into which the ulcer appeared to extend (Fig. 1 and 2). The mass encroached on the base of the duodenum and also to some degree on the medial aspect of the duodenal loop. The duodenal loop was somewhat widened as a result. The rest of the small bowel appeared to be normal.

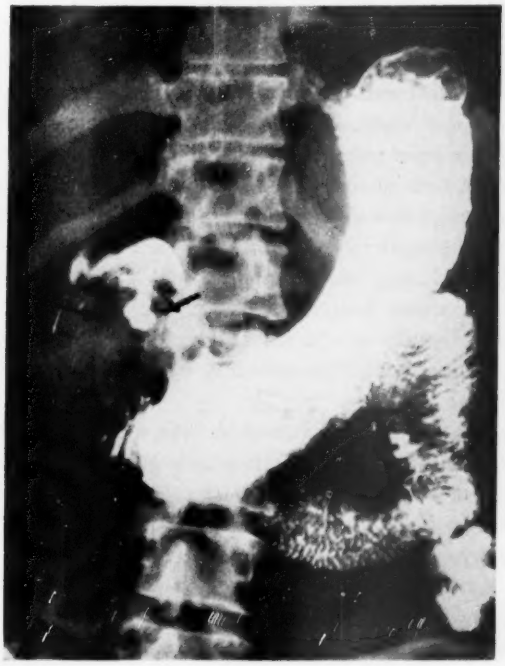

FIGURE 2. *Anteroposterior Film from the Gastrointestinal Series. Arrow on the right points to the ulceration. The two arrows on the left outline the mass pressing upon the gastric antrum.*

While in the hospital the patient showed little change in symptoms or signs. Several transfusions were given, and the hemoglobin rose to 15.3 gm. On the twelfth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ALLEN G. BRAILEY*: So far as can be judged this fifty-two-year-old housewife was well up to the

*Assistant physician, Massachusetts General Hospital.

age of forty-seven or forty-eight, when she was noted to have hypertension. The hypertension was probably of the benign type and of little significance. The only blood pressure reported in the protocol was that taken on admission several years later and was within the normal range. Three years before admission she spent a year in bed because of a "fatigued heart." This seems an extraordinary statement. Presumably, if an active woman consented to stay in bed for an entire year, she must have been really sick or badly frightened. Yet at the time of admission to the hospital there were very few signs or symptoms of primary cardiac disease. The heart was not enlarged on physical examination or x-ray study. She did complain of weakness and had a rapid pulse, but these findings were adequately explained by the anemia. I doubt if she had any serious heart disease, and I do not know why she was thought to have had heart disease three years before having been seen here.

It seems likely that the entire present illness was directly related to the disease that had caused an ulceration of the stomach. May I see the x-ray films?

Dr. John F. Gibbons: A huge ulceration of the stomach in the prepyloric area is quite apparent on all these films (Fig. 1). It seems to be on the posterior wall of the stomach in relation to the soft-tissue mass that was described (Fig. 2). This mass is causing some pressure on the medial side of the duodenal loop, producing widening and compression of this structure. The remainder of the stomach appears to be normal, and there is no calcification in this area. One may postulate either that the ulceration has extended from the stomach into the mass or that it has extended from the mass into the wall of the stomach.

Dr. Brailey: Can you see whether the mass is external to the stomach?

Dr. Gibbons: I think it is extrinsic to the antral portion of the stomach.

Dr. Brailey: I am going to assume that the patient had an ulcer of the stomach wall that had resulted in transient perforation one month before admission and perhaps also three months before admission. Other explanations are possible but at least it may be true that the daily fever and sweats were due to localized peritonitis and abscess formation. The severe anemia was of a type characteristic of chronic blood loss, and presumably this blood loss was due to oozing from the ulcer bed. This suggestion is partly substantiated by the finding of occult blood in the stools.

Was this lesion a benign, callous ulcer? Certainly, benign ulcer cannot be excluded; however, there are several arguments against it. Benign ulcer would ordinarily give a long history of recurrent symptoms whereas this woman seems not to have had digestive symptoms until three months before admission—that is, unless one wishes to suppose that the symptoms that let to cholecystectomy two years previously were actually due to an active peptic ulcer. The symptoms during the presenting illness were not typical of those of benign peptic ulcer. More important is the fact that benign gastric ulcer is a rare disease in women and finally that the lesion was located in the prepyloric region — an area where the odds favor ulceration of a pre-existing cancer of the stomach. No test for gastric acidity was reported. I wonder if one was made.

Dr. Winfield S. Morgan: There is no mention of it in the record.

Dr. Brailey: This is a case in which such a test would have been of real help. The character of the bleeding was perhaps a clue. In general, benign ulcer is likely to cause massive hemorrhage; oozing is somewhat more suggestive of cancer. It seems the part of better judgment to suppose that this ulcer occurred in a pre-existing neoplastic lesion. Any neoplastic lesion of the stomach may ulcerate. Leiomyosarcoma, lymphoma and carcinoma are very likely to do so. There seems no valid reason in this case to reject carcinoma for diseases that are much less frequent in occurrence.

The information was offered that this woman was exposed to tuberculosis, but tuberculosis of the stomach is exceedingly rare and probably is seldom diagnosed.

I should consider the possibility that the carcinoma actually arose in the pancreas and later invaded the stomach wall. This sequence of events is reported from time to time. Free hydrochloric acid in the stomach would favor such a diagnosis; however, I do not have that information. Primary disease of the pancreas is suggested by the widening of the duodenal loop, by the complaint of pain in the back and by phlebothrombosis, which I take to have been the reason for the area of tenderness on the medial aspect of the left thigh.

I confess to a real temptation to make as the final diagnosis carcinoma of the pancreas, with

invasion of the stomach—partly, perhaps, because the cases taken up at these conferences may be unusual rather than run-of-the-mill. However, one should not let one's clinical judgment be swayed by an increased likelihood of the exotic in these exercises, and I believe these data call for the diagnosis of carcinoma of the stomach, with ulceration, perforation, hemorrhage and abscess formation.

DR. GORDON A. DONALDSON: When this woman was on the medical service, we wondered whether she had a benign or a malignant ulcer. The nature of the bleeding suggested a malignant process. On the other hand the lesion, we had thought, was in the duodenum and therefore more likely benign. I believe our preoperative diagnosis was carcinoma of the duodenum.

CLINICAL DIAGNOSIS

Carcinoma of duodenum.

DR. ALLEN G. BRAILEY'S DIAGNOSIS

Carcinoma of stomach, with ulceration, perforation, hemorrhage and abscess formation.

ANATOMICAL DIAGNOSIS

Squamous-cell carcinoma of pancreas, with extension to and ulceration of duodenum.

PATHOLOGICAL DISCUSSION

DR. DONALDSON: At operation there was so much edema in the pyloric portion of the stomach and in the duodenum that we believed that this area should not be resected at this time, and a "first-stage" gastrectomy was done, defunctioning the distal stomach and duodenum. In addition there was some adherence of the hepatic flexure to the mass, and an ileotransverse colostomy was done.

DR. BRAILEY: Where did you think the ulcer was?

DR. DONALDSON: At operation we believed that the actual site of the primary disease was immediately beyond the pylorus.

DR. BRAILEY: Why did the radiologists think it was prepyloric?

DR. GIBBONS: I still think it appears to have been prepyloric rather than duodenal. I should not think, from these films, that it arose in the duodenum. The pyloric canal seems to lie distal to the large ulcer crater; however, it may be that there was gross deformity of the duodenal bulb and that the pyloric canal lay proximal to the crater. I should not have suspected that.

DR. DONALDSON: There was marked edema in this region that had distorted the pylorus.

DR. GIBBONS: There may be so much distortion that the actual relation of the pylorus to the ulcer is not clear.

DR. DONALDSON: Two weeks later when we did the second procedure, the tissues were less edematous and much more easily handled, and the bleeding was more readily controlled, so that it was possible to resect the entire area, including a 4-cm. segment of the superior mesenteric vein.

DR. MORGAN: The specimen we received from the first operation consisted of a sleeve-like resection of the stomach that was not involved by tumor and was otherwise perfectly normal. The specimen removed at the second operation consisted of the head and part of the body of the pancreas, the duodenum and portions of ileum, common duct and large bowel. The head of the pancreas measured about 5 cm. in diameter and was replaced by firm tumor, which had extended into the duodenum, forming a large ulcer measuring about 5 cm. across, and into the large bowel, forming a smaller ulceration about 0.7 cm. across. Microscopically, this proved to be an interesting tumor, a well differentiated squamous-cell carcinoma.

Squamous-cell carcinoma in this region is quite unusual, the vast majority of tumors being adenocarcinoma. The exact origin of this type of tumor is not known, but it has been postulated that primary squamous-cell carcinomas in this area originate in areas of squamous metaplasia, perhaps in the duct of the pancreas. We carefully examined several random sections of pancreas in this case looking for squamous metaplasia but were unable to find any.

DR. GIBBONS: Was any of the stomach involved by the tumor? Did it grow into the antral portion of the stomach?

DR. MORGAN: No.

DR. DONALDSON: I think it is of interest that all 9 lymph nodes were negative.

DR. BRAILEY: What was the ulceration noted initially due to?

DR. DONALDSON: In retrospect I think that distortion of the prepyloric area was due to edema, the base of the duodenal cap being visualized.

DR. GIBBONS: I suppose so. This was an ulceration of the duodenum?

DR. DONALDSON: Yes; the tumor invaded the duodenal wall, producing mucosal ulceration.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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THE STRUGGLE EVERLASTING

WALTER LIPPMANN,* speaking earlier this year at the annual dinner of the Harvard Club of Washington, gave his own unalterable concept of the current struggle between the so-called free world and that dominated by the doctrines of communism. His concept is not that of a struggle between opposing factions of a single generation; it is that of one between two types of thought that will go on indefinitely, generation after generation, like the conflict between Christianity and Islam, which has been waged for a thousand years and is still not finished.

*Lippmann, W. Present balance of power. *Harvard Alumni Bull.* 55:590-593, 1953.

The present division of the world also is one based not entirely on two forms of government or on political or economic differences that changing conditions might settle, nor is it between two utterly inharmonious religious forces. It is rather between religion and the lack of it, or between a belief in and a reliance on a higher power than man, and a belief in the capacity of men relentlessly to regulate their own actions and achieve their own mutual destiny at a dead level on which almost all are supposed to share equally in the rewards, however meager, and above which a few only are permitted to rise.

Democracy, as a form of government that has the sanction of all or nearly all who live under it, is the form embraced by all or nearly all the countries opposed to communism. Democracy, unfortunately, although it has the strength inherent in freedom has also the weaknesses of freedom — a diffusion of energy, a distaste of working co-operatively, a tendency to excessive bureaucracy and the usual confusion between sound leadership and the brassy vocalism of demagoguery.

Mr. Lippman, believing that neither side in so vast and protracted a struggle dares resort to a military decision, is of the opinion that the contest has passed into a phase bearing "some resemblance to the older procedures of diplomacy." In this respect the United States has started badly, and he predicts a singular lack of success if, when we urgently need to do well, "before our diplomats can go to their posts of responsibility, they must be taken out into the public square, beaten, kicked, spat upon, and then dragged through the sewers."

It is his conviction that a country that permits its public servants to be treated that way will not deserve to win a political war "of which the ultimate stakes are the confidence and faith of mankind in reason, justice, liberty and ordinary human decency."

The country will probably receive about what it is willing to accept in the behavior of the representatives that it selects. If standards are to be high it will be because high standards are demanded. High standards, if they should be the people's choice, would sharpen the differences between friends who are presumably dedicated to decency

in their relations and foes who know no such distinctions. Physicians as individuals and as a strategically placed group may by their influence, if they will accept the responsibility, play a part in helping to maintain their country's relations on a dignified and respected level.

POLIOMYELITIS PREVENTION AND GAMMA GLOBULIN — A REORIENTATION

THE papers recently presented by Hammon and his associates[1-3] offered conclusions on the result of careful field studies made in poliomyelitis-epidemic areas in Utah, Texas, Iowa and Nebraska. The conclusions drawn by these authors were that Red Cross gamma globulin "was shown to give highly significant protection against paralytic poliomyelitis," both in reducing the incidence of paralysis and in "significantly modifying the severity" in cases occurring during the first week after the injection of gamma globulin. These conclusions were reached after a study of 54,772 children between the ages of one and eleven, half of whom were given the gamma globulin and half a gelatin as control. The period of follow-up study was thirteen weeks, and the greatest care was taken to avoid errors in reporting. Among this group of children 104 contracted paralytic poliomyelitis, 73 in the control group and only 31 in the group receiving gamma globulin. The difference in severity of paralysis in the two groups is based on 12 gamma-globulin-treated cases as against 16 in the control group. The authors concluded from this that the calculated difference was so in favor of the former that the benefit was obvious without the use of controls and, further, that 42 cases of paralytic poliomyelitis were prevented in the gamma-globulin-treated cases.

Unfortunately, these conclusions have led to widespread publicity in the lay press, the radio and television, especially during the drives for the March of Dimes and the Red Cross.

The careful field work carried out by Dr. Hammon and his associates was admirable. The conclusions drawn from the 104 cases are open to serious criticism on the basis of biostatistics. The history of measures used in the treatment and prophylaxis of poliomyelitis is full of conclusions based on inadequate material and subsequently proved to be erroneous. Although gamma globulin may offer a protection against poliomyelitis the results in these 104 cases cannot be taken as a satisfactory evaluation of such protection. On the surface this report favors gamma globulin, and if similar results had been found in five times as many cases such conclusions as were drawn would be "highly significant."

The manifestations of infectious diseases are always variable, whether they are the rash of streptococcosis, the whoop in whooping cough, the salivary-gland involvement of mumps, or the paralysis in poliomyelitis. Indeed, the paralysis in poliomyelitis as a variable is more akin in its incidence to otitis media in streptococcosis and to orchitis in mumps. For it is well to bear in mind that the site of the paralytic lesion in poliomyelitis is as remote from the site of the original invasion as a mastoiditis in scarlet fever or an orchitis in mumps. Although the actual incidence of paralysis in poliomyelitic infection is unknown, there is ample evidence on epidemiologic grounds that it varies widely in incidence and severity. It is the variation in incidence that requires at least 500 cases to offer satisfactory biostatistical evidence.

To attempt to evaluate a preventive measure on the basis of 100 cases is precarious in any infectious disease, and more especially so in poliomyelitis, in which even the nonparalytic form is a presumptive diagnosis without virus studies. Consequently, it appears that the use of gamma globulin as a prophylactic agent against poliomyelitis demands further study before it is accepted as a proved measure.

It is unfortunate that the National Foundation for Infantile Paralysis should put out a brochure entitled: "Polio Message to Parents, Gamma Globulin 1953," which reads in part, "In 1952 March of Dimes scientists proved it to be an effective but temporary preventive of crippling caused by polio," and later, "Polio vaccines are still in the experimental stage." The contrast of these two statements could react unfavorably on further investigative efforts in vaccines, which offer the greatest promise as a public-health measure against poliomyelitis.

The die has been cast. The demand for gamma globulin exists. This product will be supplied to physicians so far as the allotment to each state permits. It is to be hoped that the medical profession will co-operate fully in an investigative spirit with the requirements laid down so that the true value of this agent can be assessed. Furthermore, much can be done to prevent panic by emphasizing the experimental basis in the present situation.

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STUDYING THE COMMON COLD

As the country prepares to be parboiled, braised and baked in the expected simmering heat of another North American summer, it must also look forward to the aftercoming fall when the first frost puts in its appearance, school sessions begin and noses start to run. For the common cold is as inevitable as taxes, and despite ample discussion little that seems to be effective has been done about either.

The common cold, nevertheless, the destroyer of efficiency even if no great taker of lives, has had its share of scientific investigation. The fruitlessness of much of this research points up the difficulties that are encountered in the study of this particular type of infection. The failure to establish the cold virus in ordinary laboratory animals has made it necessary to use human volunteers, with all the limitations that such studies entail — limitations that have emphasized the desirability of further efforts to develop effective laboratory methods for the identification and appraisal of these agents.

Many secondary problems are involved, including the clinical differentiation of the common cold from various similar disorders such as the early stages of a number of specific infections, allergic conditions and those resulting from toxic irritants.

Recent attempts at the differentiation of these causes of rhinorrhea have been based on the cytologic and microbiologic study of the nasal secretions of normal persons and those suffering from a variety of upper respiratory tract disorders. The methods employed have included differential studies of the cells found in stained smears of the secretions, cultures for bacterial determinations, and inoculations of nasal secretions and throat washings into embryonated eggs.

Investigative procedures proposed for the continuation of this work include the assembling of further data along the above lines and attempts to grow the virus on tissue-culture mediums, as has been done with influenza virus. Recent advances in virology have been so notable that the eventual conquest of the ubiquitous cold seems inevitable.

Turpentine in Haemoptysis. — *Long experience has taught Dr. Lange (of Koenigsberg) that the spirit of turpentine acts more promptly in haemoptysis than the different methods usually employed in the affection, such as tannin, common salt, acetate of lead, alum, nitrate of potash, cold applications and leeching.*

Boston M. & S. J. *July 13, 1853*

MASSACHUSETTS MEDICAL SOCIETY

SECRETARY'S LETTER

To the Fellows of the Society: This letter is addressed to you only if you are one of the 2000 who have not seen fit to retain membership in the American Medical Association. Perhaps you have overlooked the bill for your dues. If so, you are penalizing your more conscientious fellows by depriving them of effective representation in the larger association.

Many nonpracticing physicians have no immediate personal interest in the practice of medicine or its problems, and so excuse themselves from participation in an organization that nevertheless represents all doctors of medicine and is devoted to the larger cause of improving medical care. Some nonmembers are no doubt mavericks who are constitutionally unable to participate in any democratic organization. A considerable group, important because of their better-than-average training, skill and achievements, if not because of their numbers, have a distaste for what they consider the crass methods and attitudes of organized medicine.

If the ideas of spokesmen for the American Medical Association do not represent your point of view, it is because you have withdrawn from participation in the formation of those ideas. If you object to a specific action or statement emanating from the American Medical Association, you should so inform your delegate, rather than write a piece for the *Literary Review* or make an indignant speech before the Young People's Society of your church.

To resign from a democratic organization because it has opinions with which you do not agree is not an effective way of correcting those opinions. Neither is it a courageous act. Dissenters should not pettishly quit the group to which they belong because they do not like its platform. They should stand up and be counted.

Be courageous; mail in your $25 A. M. A. membership fee. Then find out what the American Medical Association is really doing.

ROBERT W. BUCK, M. D.
Secretary

SECRETARY'S NOTE

The *Directory* of the Massachusetts Medical Society, which is the basis for our mailing list and that of the *New England Journal of Medicine*, is under constant revision.

Notices of changes of address should be sent directly to the Secretary, 22 Fenway, Boston 15, rather than to any intermediary agent, if prompt correction in the mailing list is to be made. The office address should be clearly distinguished from the residence address and it should be indicated which one is to be used for mailing purposes. When a fellow moves out of the State, he should let us know whether the move is temporary or permanent.

Fellows are urged to notify this office if they do not receive communications from the Society promptly or regularly. It is to be remembered, however, that delays and errors sometimes occur in delivery even though our mailing list is correct.

If the *Proceedings* of the Council, the *New England Journal of Medicine* or even the news bulletin published in the local district is not received, fellows are invited to communicate with the Secretary of the Massachusetts Medical Society.

ROBERT W. BUCK, M.D.
Secretary

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

USE OF POLIOMYELITIS-IMMUNE GLOBULIN

The decision to use poliomyelitis-immune globulin this year is based upon the work of Hammon and his associates in Utah, Texas, Iowa and Nebraska. There is a difference of opinion about whether his evidence was strong enough to justify widespread use of the product. However, it was decided at a conference of state and federal authorities that poliomyelitis-immune globulin should be made available for use on a country-wide basis as a possible means of prophylaxis.

In attempts to apply methods suggested by Hammon's studies to the prevention of paralytic poliomyelitis this summer certain fundamental points must be kept in mind. It must be understood that the studies were made in the presence of frank epidemics. Only about 10 per cent of all cases occur under such conditions. This year's program is attempting to reach also the cases occurring in non-epidemic areas. It is yet to be determined whether the results will be better or worse when the globulin is used under different circumstances.

The expected number of paralytic cases of poliomyelitis that can be prevented in the coming summer is small, probably not more than 10 for the State. It is essential, therefore, that the procedures adopted be those best designed to give the greatest possible service.

It is particularly important that it be clearly understood by all that poliomyelitis-immune globulin gives only a passive, temporary type of immunity, not the more lasting, active immunity produced by vaccines. If a safe and effective vaccine is produced, there will be little place for gamma globulin in the prevention of poliomyelitis.

A limited supply of poliomyelitis-immune globulin (gamma globulin that has been tested for poliomyelitis Type 2 antibodies) will be made available for the use of physicians during the coming poliomyelitis season. The material is obtained by the National American Red Cross and the National Foundation for Infantile Paralysis and allocated to each state health department through the Office of Defense Mobilization.

RESPONSIBILITY OF STATE HEALTH DEPARTMENT

A communication from the Office of Defense Mobilization states: "The State or Territorial Health Officer shall have full responsibility for the distribution of poliomyelitis immune globulin allocated to him. He shall decide the modes of prophylaxis which are most appropriate for use within his jurisdiction."

The Department has agreed to assume responsibility for the distribution of poliomyelitis-immune globulin. A committee on allocation of poliomyelitis-immune globulin was formed by request of the Commissioner of Public Health, with representatives of medical, health and citizens' organizations. The Committee has considered the guidance found in reports of the National Committee of Experts and has arrived at the following plans for the use of the supply of poliomyelitis-immune globulin available to Massachusetts.

General Considerations

Gamma globulin is a well established preventive means in measles and hepatitis. The national supply for this purpose is threatened if unwarranted use is made of it in poliomyelitis. Only gamma globulin that is labeled poliomyelitis-immune globulin should be used in attempted prevention of poliomyelitis, so that the need in measles and hepatitis can be filled by the supply allotted for this purpose.

State Allotment of Poliomyelitis-Immune Globulin

The basic state allotment equals 60 cc. times the average annual number of reported cases of poliomyelitis in the five-year period, 1947–1951. Since that average is about 600 for Massachusetts, 3600 10-cc. doses will be available. Unusually high incidence in 1953 will constitute basis for further allotment.

Basic Plan for Distribution

Household contacts of a patient with poliomyelitis have at least a ten-fold greater chance of contracting the disease than any other group of people. Roughly, 1 out of 100 household contacts are attacked, in contrast to the risk of 1 out of 1000 to 10,000 in various other epidemic situations. Approximately the same risk prevails in a summer camp in which a case of poliomyelitis develops. Hence, the rationale would be to apply immune globulin to household and camp contacts as soon as possible after a case is diagnosed.

It is evident that the state allotment does not reach further than supplying about 6 persons in the immediate proximity of each expected case of poliomyelitis. The physician has the responsibility of selecting persons who are the greatest risk and of establishing the diagnosis of the index case as early and accurately as possible.

Criteria for Diagnosis

A national committee has recommended that the minimum for the diagnosis of poliomyelitis should be at least three of the following: history compatible with poliomyelitis; fever; stiff neck or stiff back, or both; 10 to 500 leukocytes per cubic centimeter of spinal fluid taken during the acute or early convalescent period; spinal-fluid protein elevated above normal limits; and demonstrable muscle weakness or paralysis.

Persons to Whom Gamma Globulin May Be Given

Poliomyelitis-immune globulin will be made available for the following household contacts: all persons under thirty years of age and all pregnant women living in the same household (apartment or one-family house or camp) as the patient; and persons sleeping in other quarters but remaining during the day in the home of a patient for a considerable time, who may be included (the physician will have to use utmost caution not to include more than one or two of this kind in the group).

Community-wide injection may be authorized in a limited area with high incidence, if additional immune globulin can be obtained from the national supply for this purpose. The critical incidence is established from time to time on a national level. Only children under sixteen years would be given the globulin under such circumstances.

Physician's Request

To obtain poliomyelitis immune globulin for the household contacts of a patient, a physician must supply to the distribution station the name and age of the patient and the date of onset of the poliomyelitis, as well as the names and ages of the contacts to whom he proposes to give the product. Forms will be available at distribution stations and boards of health for making such requests. Although the request will be accepted on the physician's letterhead or other paper, it is well to use the form if possible to avoid delay because certain information may be missing.

The original stock will be replaced only when these requests are forwarded to the Institute of Laboratories. Vials removed from the distribution station without such a record will not be replaced.

Amounts to Be Issued

The distribution station will issue poliomyelitis-immune globulin on the physician's request in appropriate amounts, as shown in Table 1.

Table 1. *Schedule of Amounts to Be Issued.*

Age of Contact	Amount cc.
Under 6 mo.	2
6 mo. through 2 yr.	3
3 yr. through 20 yr.	1 (per year)
21 yr. through 29 yr.	20
Pregnant women	20

These amounts are based upon the recommended dosage of approximately 0.14 cc. per pound of body weight.

Report on Use By Physician

Each physician who gives immune globulin to contacts of reported cases will be expected to fill out a brief report, noting any illness that occurs among those injected during the next three weeks.

The best hope of determining the value of gamma globulin as used this year will be to collect complete information regarding the cases that occur in household contacts. The report of the physician is to help in unearthing any additional occurrences of multiple cases in the household that might otherwise be missed.

Records on Reported Cases

Each reported case of poliomyelitis will be investigated epidemiologically by health departments. Case records will disclose which patients have received prophylactic poliomyelitis-immune globulin and other information to aid in evaluating the product.

Distribution Stations

Supplies of poliomyelitis-immune globulin will be placed in only a few strategically located areas. The following list includes the stations for distribution of the product:

DISTRIBUTION STATIONS FOR POLIOMYELITIS-IMMUNE GLOBULIN

County	Station*
Barnstable	Hyannis — Cape Cod Hospital
Berkshire	Great Barrington — V.N.A., 54 Castle Street North Adams — Health Department, City Hall, 14 Summer Street Pittsfield — Board of Health Laboratory, 44 Durham Street
Bristol	Attleboro — Sturdy Memorial Hospital, Park Street Fall River — Board of Health New Bedford — Board of Health Taunton — Board of Health, City Hall
Dukes	Oak Bluffs — Martha's Vineyard Hospital
Essex	Beverly — Board of Health, 191 Cabot Street Haverhill — Board of Health, 471 Main Street Lynn — Board of Health, City Hall
Franklin	Greenfield — Franklin County Hospital
Hampden	Holyoke — Board of Health Palmer — Wing Memorial Hospital, Wright Street Springfield — Board of Health, City Hall
Hampshire	Northampton — Board of Health
Middlesex	Ayer — Nashoba Associated Boards of Health, Community Memorial Hospital Cambridge — Board of Health, City Hall Framingham — Board of Health, Memorial Building Lowell — Health Department Waltham — Health Department Woburn — Health Department
Nantucket	Nantucket — Nantucket Cottage Hospital
Norfolk	Franklin — Board of Health Quincy — Health Department
Plymouth	Abington — No. Abington — Bemis Drug, 185 North Avenue Plymouth — Health Department, Town Square
Suffolk	Boston — Health Department Biologic Laboratories, 375 South Street, Jamaica Plain
Worcester	Athol — Board of Health, 599 Main Street Clinton — Board of Health, 242 Church Street Fitchburg — Board of Health Gardner — Board of Health Webster — Board of Health, Municipal Building Worcester — Board of Health, City Hall

*When poliomyelitis becomes highly prevalent in a community not on this list, the Department may authorize the establishment of a special distribution station for the duration of the high prevalence.

SEROLOGIC DIAGNOSIS OF TOXOPLASMOSIS

A laboratory service is now available through the Communicable Disease Center Laboratory of the Public Health Service in Chamblee, Georgia, for the serologic diagnosis of toxoplasmosis. The laboratory is performing the Sabin–Feldman methylene blue dye-test at present.

In accordance with the policy of the Communicable Disease Center, physicians in the Commonwealth should submit specimens to the Diagnostic Laboratory, 281 South Street, Jamaica Plain 30, which will forward them to the Center. Until further information becomes available on the interpretations of serologic tests, specimens are being accepted only from patients with suspected cases of congenital toxoplasmosis, because only on such cases can the results of serologic tests be reliably interpreted under present knowledge. Serums from both mother and child should be submitted if possible. Serums from adults with suspected postnatal toxoplasmosis are not accepted at present.

Certain information is required with each specimen, including name of patient, age, sex, date of onset of illness, date blood drawn, the particular clinical manifestations suggesting the possibility of toxoplasmosis, and the preservative if any added. (No preservative is recommended, but knowledge of any added is necessary.) Forms for submitting specimens may be obtained promptly on application to the Diagnostic Laboratory (JA 2-3700).

Diagnosis of Congenital Toxoplasmosis by Serologic Methods*

The diagnosis of congenital toxoplasmosis cannot be made in the absence of dye-test antibody in the child, regardless of how high the titer may be in the mother's serum. A positive diagnosis can be made when the dye-test titer is 1:256 or more in both the mother and child, provided the child is over four months of age. When a high titer is obtained in a child during the first weeks of life, the test should be repeated at the end of four months. If the high titer was due to infection with toxoplasma, it will be high in the second test. If the second test is negative, or the titer is low, the diagnosis of toxoplasmosis cannot be made, because the result of the first test was due to passive transfer of antibody from the mother.

When a high dye-test titer is obtained in a child during the first weeks of life, a complement-fixation test is also done on both mother and child; if the mother has high titers of both antibodies, and the child has no complement-fixing antibody, the results are indicative of a current, active infection with toxoplasma, which should be treated.† (Nevertheless, as stated above, the tests should be repeated a few months later to determine if the previously discovered antibodies were passively transferred.)

In older children, particularly over the age of six years, when the dye-test titers may be less than 1:256 in the mother or child, or in both, the diagnosis can still be regarded as highly probable if the child has clinical manifestations that are compatible with congenital toxoplasmosis.

When only the mother's serum is available for examination, because the child died before congenital toxoplasmosis was suspected, a dye-test titer of 1:256 or more does not prove that the child had toxoplasmosis, but a negative test, or a low titer, within three years of delivery indicates that the child did not have toxoplasmosis.

*Prepared by the Committee on Toxoplasmosis, Tropical Medicine Study Section, National Institutes of Health.

†On the basis of present knowledge (as of January 1, 1953), treatment with sulfonamide, to the limit of the patient's tolerance, is given for at least several weeks.

CORRESPONDENCE

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held May 28, 1953, it was voted to revoke the registration of Dr. Herman Schwartz, of Boston.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Physiologic Therapy for Obstructive Vascular Disease. By Isaac Starr, M.D., Hartzell Research Professor of Therapeutics, University of Pennsylvania School of Medicine. 8°, cloth, 38 pp., with 3 tables. New York: Grune and Stratton, 1953. $2.50. (*Modern Medical Monographs* No. 6.)

The material in this monograph was prepared for the George E. Brown Memorial Lecture and was delivered before the American Heart Association in April, 1952. The author discusses the various methods of treatment, and the conditions prevailing before 1928. There is a bibliography and an index. The publishing is excellent.

Infectious Mononucleosis. By Sidney Leibowitz, M.D., associate physician, Beth Israel Hospital, New York City. 8°, cloth, 163 pp., with 14 tables and 3 illustrations. New York: Grune and Stratton, 1953. $4.75. (*Modern Medical Monographs* No. 5.)

Dr. Leibowitz discusses the clinical, hematologic and serologic considerations of the disease. An innovation is the summaries appended to the chapters. A series of 24 case histories concludes the text. There is a bibliography of 377 items.

NOTICES

RADIOLOGIC HEALTH TRAINING PROGRAM

A series of short courses in radiologic health is again being presented by the Public Health Service at the Environmental Health Center, Cincinnati, Ohio. These courses, tuition free, are designed primarily to provide professional personnel working in health departments and other organizations with a working knowledge of the health hazards associated with radiation. Candidates should have a degree in medicine, engineering or science (physical or biologic).

Instruction is given in radiation physics sufficient for an understanding of the problems arising from proper and improper use of ionizing radiation. Laboratory and lecture periods are presented covering the hazards, and methods of alleviating these hazards, as encountered in employment of x-rays, radioisotopes, neutron fluxes and particle accelerators.

Courses are each two weeks in length. Basic courses, which stress basic radiation physics and survey technics, will be presented on the following dates: October 5–16, 1953; January 11–22, 1954; and May 3–14, 1954. The basic course or its equivalent is a prerequisite for the intermediate course. Laboratory assay of radioelements and x-ray survey technics are emphasized in the intermediate course, which will be presented on the following dates: October 19–30, 1953; January 25–February 5, 1954; and May 17–28, 1954. Completion of the intermediate course or its equivalent is a prerequisite for admission to the advanced course. This course, for professional personnel concerned in particular with occupational health problems, will be presented from February 8 to 19, 1954.

Further details and information may be obtained from the Chief, Radiological Health Training Section, Public Health Service, Environmental Health Center, Cincinnati, Ohio.

SOCIETY MEETINGS AND CONFERENCES

JULY 23–25. West Virginia State Medical Association. Page 44, issue of July 2.

AUGUST 10–16. Institute on Teaching and Improving Esophageal Speech. Page 44, issue of July 2.

AUGUST 18–21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.

OCTOBER 4–9. American Academy of Pediatrics. Page 1126, issue of June 25.

OCTOBER 17–20. American Association of Blood Banks. Page 1126, issue of June 25.

OCTOBER 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

SEPTEMBER 12–15, 1954. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18, 1954. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETY

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SEPTEMBER 23.

NOVEMBER 18.

JANUARY 20. (Combined with the Auxiliary.)

MARCH 24.

MAY 12. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 16

THURSDAY, JULY 16

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JULY 17

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JULY 18

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a. m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JULY 20

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
12:00 m. Pediatric Medical-Surgical Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, JULY 21

9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

WEDNESDAY, JULY 22

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

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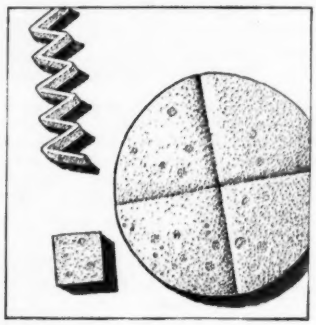

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1. Howard, J. E. Protein Metabolism During Convalescence After Trauma. Arch. Surg. 50:166, 1945.
2. Co Tui, Minutes of the Conference on Metabolism Aspects of Convalescence Including Bone and Wound Healing. Josiah Macy, Jr. Foundation, Fifth Meeting Oct. 8-9, p. 57, 1943.
3. Whipple, G. H. and Madden, S. C. Hemoglobin, Plasma Protein and Cell Protein: Their Interchange and Construction in Emergencies. Medicine 23:215, 1944.
4. Mulholland, J. H., Co Tui, Wright, A. M., Vinci, V., and Shafiroff, B. Protein Metabolism and Bed Sores. Am. Surg. 118:1015, 1943.

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1. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585-592, 1951.

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